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(54) Title: NK-1 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF EYE DISORDERS

(57) Abstract

The present invention relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, excess lacrimation, hyperemia and breakdown of the blood aqueous barrier in mammals, including humans, using an NK-1 antagonist. It also relates to a method of treating or preventing such disorders in mammals, including humans, using certain quinuclidine derivatives, piperidine derivatives, pyrrolidine derivatives, azanorbomane derivatives, ethylene diamine derivatives and related compounds that are substance P receptor antagonists.

Compound

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NK-1 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF EYE DISORDERS

The present invention relates to a method of treating or preventing a disorder of the eye selected from glaucoma ocular hypertension, miosis, excess lacrimation, hyperemia and breakdown of the blood aqueous barrier in mammals, including humans, using an NK-1 antagonist. It also relates to a method of treating or preventing such disorders in mammals, including humans, using certain quinuclidine derivatives, piperidine derivatives, pyrrolidine derivatives, azanorbornane derivatives, ethylene diamine derivatives and related compounds that are substance P receptor antagonists.

The following references refer, collectively, to quinuclidine, piperidine, ethylene diamine, pyrrolidine and azanorbornane derivatives and related compounds that exhibit activity as substance P receptor antagonists: United States Patent 5,162,339, which issued on November 11, 1992; United States Patent 5,232,929, which issued on August 3, 1993; World Patent Application WO 92/20676, published November 26, 1992; World Patent Application WO 93/00331, published January 7, 1993; World Patent Application WO 92/21677, published December 10, 1992; World Patent Application WO 93/00330, published January 7, 1993; World Patent Application WO 93/06099, published April 1, 1993; World Patent Application WO 93/10073, published May 27, 1993; World Patent Application WO 92/06079, published April 16, 1992; World Patent Application WO 92/12151, published July 23, 1992; World Patent Application WO 92/15585, published September 17, 1992; World Patent Application WO 93/10073, published May 27, 1993; World Patent Application WO 93/19064, published September 30, 1993; World Patent Application WO 94/08997, published April 28, 1994; World Patent Application WO 94/04496, published March 3, 1994; United States Patent Application 988,653, filed December 10, 1992; United States Patent Application 026,382, filed March 4, 1993; United States Patent Application 123,306, filed

September 17, 1993, and United States Patent Application 072,629, filed June 4, 1993. All of the foregoing World Patent Applications designate the United States and were filed in the U.S. Receiving Office of the PCT. The foregoing patents and patent applications are incorporated herein by reference in their entirety.

Beding-Barnekow et al. Br. J. Pharmacol. 95 (1), 259-67 (Sept. 1988) have reported that substance P is a mediator of miosis and breakdown of the blood aqueous barrier in rabbit eyes. Mandahl, A., Eur. J. Pharmacol., 114 (2), 121-27 (1985) has reported that the substance P receptor antagonist (D-Argsup 1, D-prosup 2, D-Trpsup 7 sup, sup 9, Leusup 1 sup 1)SP inhibited miosis in rabbits caused by echothiophate iodide or pilocarpine hydrochloride.

Krupin et al, Exp. Eye Res., 34 (3) 319-24 (1982) have reported that the administration of substance P into the third ventricle of rabbits resulted in a dose dependent increase in interocular pressure.

Holmdahl et al., Science, 214 1029-1031 (1981) have reported the results of studies which they state suggest that substance P or a related peptide is a neurogenic mediator of the inflammatory response in the eye, e.g., miosis (constriction of the pupil), hyperemia and breakdown of the blood aqueous barrier. Their studies showed that the substance P antagonist [D-Pro^2, D-Trp^{7,9}]SP inhibited inflammatory responses in the rabbit eye.

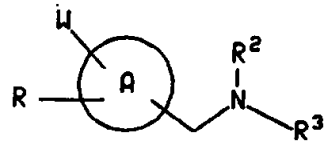
Summary of the Invention

This invention relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to such mammal an amount of a substance P receptor antagonist that is effective in treating or preventing such disorder.

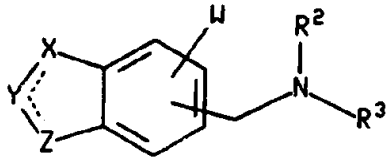
This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation

and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to such mammal an amount of a NK-1 receptor antagonist that is effective in treating or preventing such disorder.

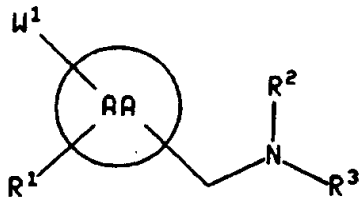
This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, and ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula



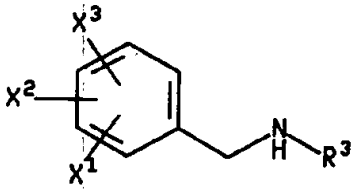
Ia



Ib



Ic



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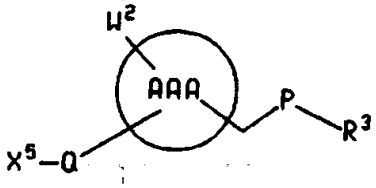


Ie

wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the sidechain containing NR^2R^3 is attached to a carbon atom of ring system A;

AA is an aryl group selected from phenyl, naphthyl, thienyl, dihydroquinolinyl and indolinyl, and wherein the sidechain containing NR^2R^3 is attached to a carbon atom of AA;

AAA is an aryl group selected from phenyl, naphthyl, thienyl, dihydroquinolinyl and indolinyl, and wherein the $-CH_2PR^3$ sidechain is attached to a carbon atom of ring AAA;

P is NR^2, O, S, SO or SO_2;

Q is SO_2, NH, $-\overset{|}{N}(C_1-C_6)$alkyl or (C_1-C_6)alkyl$-\overset{|}{N}-SO_2-$

wherein the point of attachment of said (C_1-C_6)alkyl$-\overset{|}{N}-SO_2-$ to ring AAA is the nitrogen atom and the point of attachment to X^5 is the sulfur atom;

W^1 is hydrogen, halo or (C_1-C_6) alkyl, $S-(C_1-C_3)$alkyl, halo or (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms;

W^2 is hydrogen, (C_1-C_6)alkyl, $S-(C_1-C_3)$alkyl, halo or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

W is hydrogen, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, $-S(O)_v-(C_1-C_6)$ alkyl wherein v is zero, one or two, halo or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally

substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)-alkyl-$\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$ alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-NH\overset{O}{\overset{\|}{C}}H$ and $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)$ alkyl;

X^5 is a four to six membered heterocyclic ring containing from one to three heteroatoms selected from sulfur, nitrogen and oxygen (e.g., thiazolyl, pyrrolyl, thienyl, triazolyl, oxazolyl, oxadiazolyl, thiadiazolyl or imidazolyl), wherein said heterocyclic ring may optionally be substituted with from one to three substituents, preferably with from zero to two substituents, independently selected from phenyl, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms and halo;

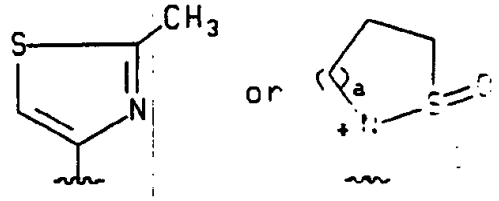
R is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, or oxazolyl) wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms;

R^1 is selected from amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, $-S(O)_v-(C_1-C_{10})$-alkyl wherein v is zero, one r two, $-S(O)_v$-aryl wher in v is zero, one or two, -O-aryl, $-SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, $(C_1-$

C_6)alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6

carbons, $-NHC(C_1-C_6)$alkyl, $-NHCCF_3$, (C_1-C_{10})alkyl$-N(-SO_2-(C_1-C_{10})$alkyl wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and $(C_1-C_{10})alkyl-N(-SO_2-aryl$; and wherein the aryl moieties of said $-S(O)_v$-aryl, -O-aryl and $(C_1-C_{10})alkyl-N(-SO_2-aryl$ are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;

or R^1 is a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the $R^2R^3NCH_2$ side chain;

the dotted lines in formula Ib represent that one of the X-Y and Y-Z bonds may optionally be a double bond;

X is selected from =CH-, $-CH_2-$, -O-, -S-, -SO-, $-SO_2-$, $-N(R^4)-$, -NH-, =N-, $-CH[(C_1-C_6)alkyl]-$, $=C[(C_1-C_6)alkyl]-$, $-CH(C_6H_5)-$ and $=C(C_6H_5)-$;

Y is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2-$, $=C[(C_1-C_6)alkyl]-$, $-CH[(C_1-C_6)alkyl]-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, =N-, -NH-, $-N(R^4)-$, =C(halo)-, $=C(OR^4)-$, $=C(SR^4)-$, $=C(NR^4)-$, -O-, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)-$ and $-CH(C_6H_5)-$ may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of

said =[(C_1-C_6)alkyl]- and -CH[C_1-C_6)alkyl]- may optionally be substituted with from one to three fluorine atoms;

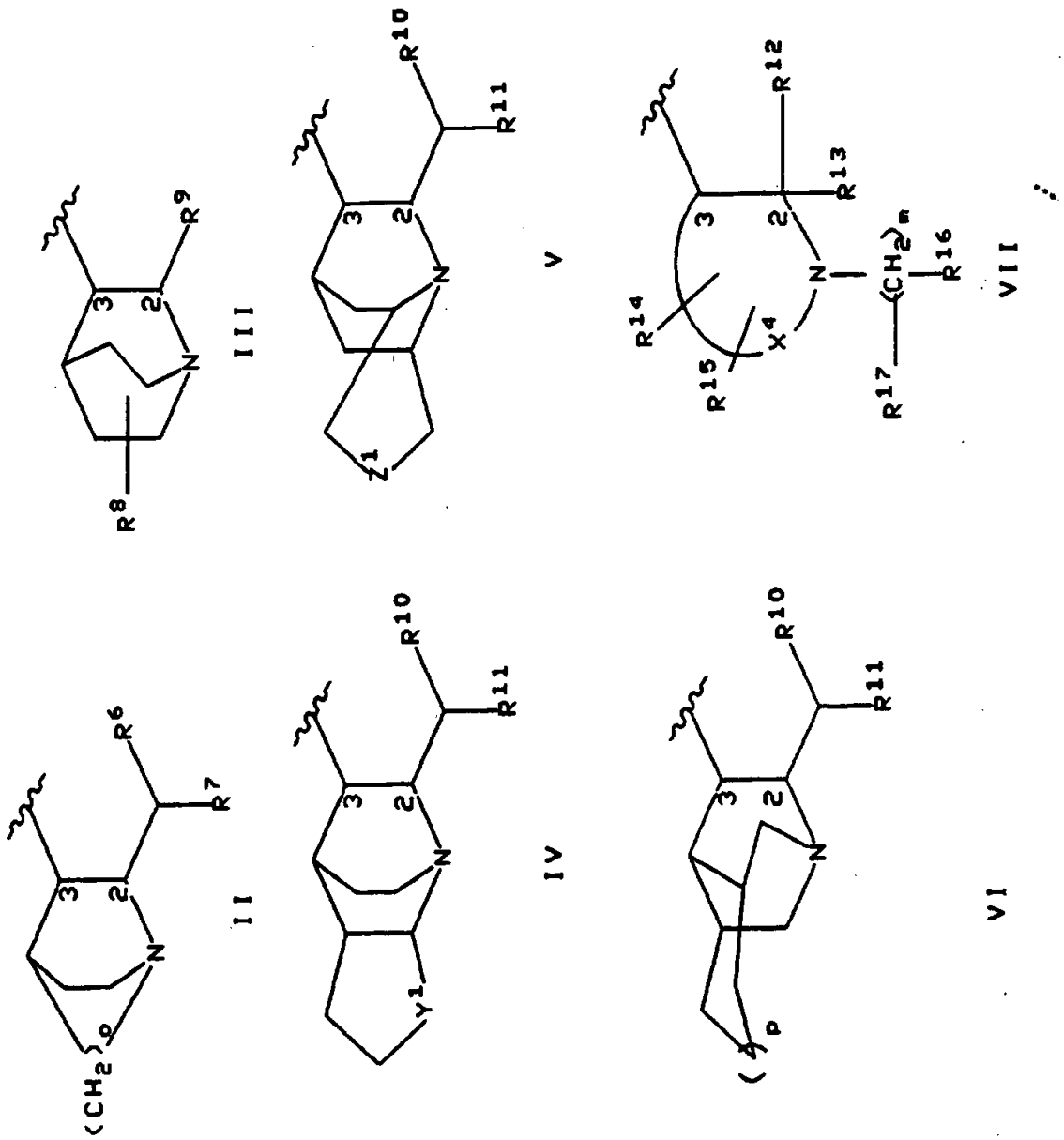
Z is selected from =CH-, $-CH_2-$, =N-, -NH-, -S-, $-N(R^4)-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, =C[(C_1-C_6) alkyl]- and -CH[(C_1-C_6)alkyl]-;

or X, Y and Z, together with the two carbon atoms shared between the benzo ring and the XYZ ring, form a fused pyridine or pyrimidine ring;

R^4 is (C_1-C_6) alkyl or phenyl;

R^2 is hydrogen or $-CO_2(C_1-C_{10})$alkyl;

R^3 is selected from


II
III
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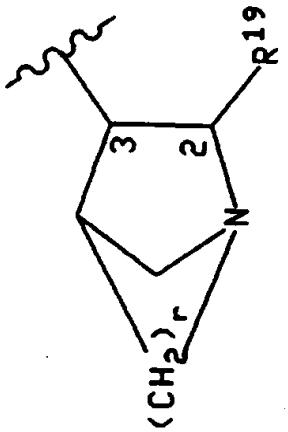
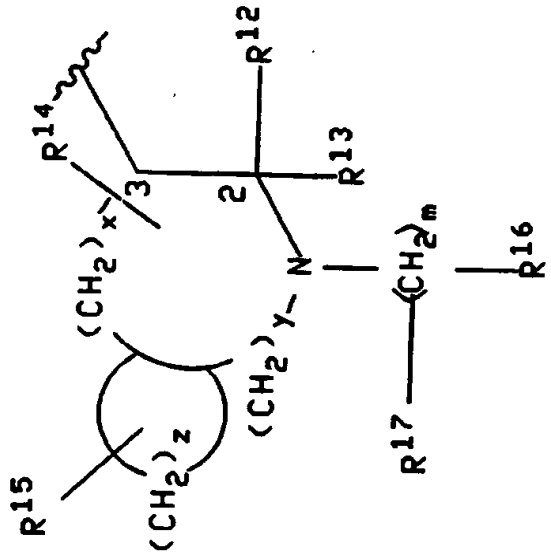
VII



IX

and



VIII

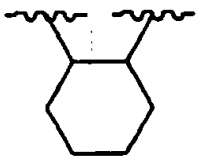
wherein R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl, wherein said phenyl may optionally be substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

R^7 is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^6;

R^8 is hydrogen or (C_1-C_6) alkyl;

R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y^1 is $(CH_2)_l$ wherein l is an integer from one to three, or Y^1 is a group of the formula



(J)

;

Z^1 is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

x is an integer from zero to four;

y is an integer from zero to four;

z is an integer from one to six, wherein the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbons of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

o is two or three;

p is zero or one;

r is one, two or three;

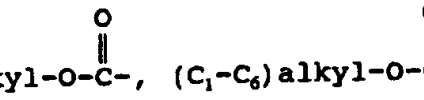
R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

X^4 is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};

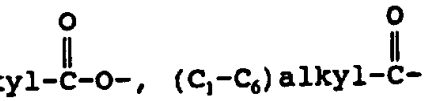
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};

R^{12} is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7)cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10})alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10})alkoxy optionally substituted with

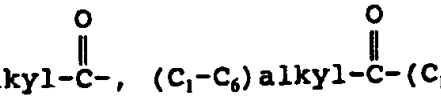
from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino,



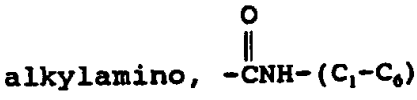
(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl,



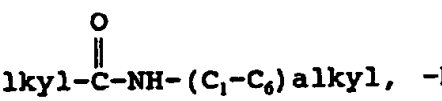
(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,



(C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-,



di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl,

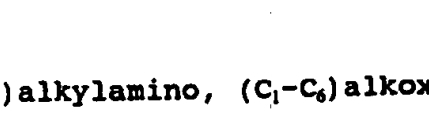


(C_1-C_6)-alkyl-C-NH-(C_1-C_6)alkyl, -NHCH and -NHC-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

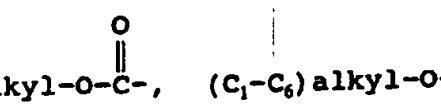
R^{13} is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to it may optionally be replaced by oxygen, nitrogen or sulfur;

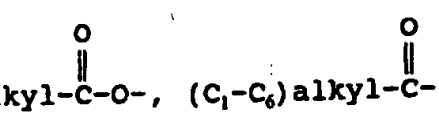
R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino,



di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C-OH,



(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl,



(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,

(C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^{12};

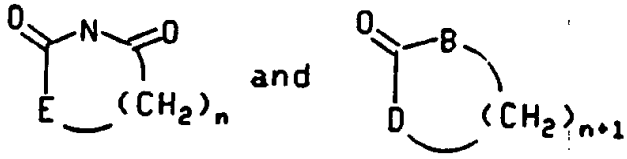
R^{16} is $NHCR^{18}$, $NHCH_2R^{18}$, SO_2R^{18}, GR^{20} CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};

R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and

R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

G is selected from the group consisting of CH_2, nitrogen, oxygen, sulfur and carbonyl;

R^{20} is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen, and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; and any one of the carbons of the $(CH_2)_n$ or $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl, and either any two of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbons of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon

atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula VIII, R^{14} and R^{15} cannot be attached to the same carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, (C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} cannot both be hydrogen; (e) when R^{14} or R^{15} is attached to a carbon atom of X^4 or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom; and (f) neither R^{14}, R^{15}, R^{16} nor R^{17} can form a ring with R^{13};

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

The fused bicyclic nucleus of compounds of the formula Ib to which W and the $-CN_2NR^2R^3$ sidechain are attached may be, but is not limited to one of the following groups: benzoxazolyl, benzthiazolyl, benzimidazolyl, benzisoxazolyl, benzoisothiazolyl, indazolyl, indolyl, isoquinolinyl, benzofuryl, benzothienyl, oxindolyl, benzoxazolinonyl, benzthiazolinonyl, benzimidazolinonyl, benzimidazoliniminyl, dihydrobenzothienyl-S,S-dioxide, benztriazolyl, benzthiadiazolyl, benzoxadiazolyl, and quinazolinyl.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (1) through (47A) below, or a

pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(1) A compound of the formula Ia or Ib wherein the substituents at positions "2" and "3" of the nitrogen containing ring of R^3 are in a cis configuration. (When R^3 is a group of the formula VII or VIII, "a cis configuration", as used herein, means that the non-hydrogen substituent at position "3" is cis to R^{12}).

(2) A compound of the formula Ia wherein R^3 is a group of the formula III, VII or IX; R^2 is hydrogen; A is phenyl or indolinyl; W is (C_1-C_3)alkoxy optionally substituted with from one to five fluorine atoms; and R is thiazolyl, imidazolyl, thiadiazolyl, pyrrolyl or oxazolyl, and R may optionally be substituted with one or two (C_1-C_3) alkyl moieties.

(3) A compound of the formula Ib wherein R^3 is a group of the formula III, VII or IX; R^2 is hydrogen; the fused bicyclic ring system to which W and the $-CH_2NR^2R^3$ sidechain are attached is benzoxazolyl, benzisoxazolyl, benzthiazolyl or benzimidazolyl; and W is (C_1-C_6)alkoxy optionally substituted with from one to five fluorine atoms.

(4) A compound as defined in paragraph 1, 2 or 3 above wherein: (a) R^3 is a group of the formula III and R^9 is benzhydryl; (b) R^3 is a group of the formula VII, R^{12} is phenyl, each of R^{13}, R^{14}, R^{15} and R^{16} is hydrogen, m is zero and X^4 is $-(CH_2)_3-$; or (c) R^3 is a group of the formula IX, r is two and R^{19} is benzhydryl.

(5) A compound of the formula Ia wherein: (a) R^3 is a group of the formula III wherein the substituents at positions "2" and "3" of the nitrogen containing ring are in the cis configuration, R^9 is benzhydryl and A is phenyl; or (b) R^3 is a group of the formula VII wherein R^{12} and the substituent at position "3" of the nitrogen containing ring are in the cis configuration, A is phenyl, R^{12} is phenyl, each of R^2, R^{13}, R^{14}, R^{15} and R^{16} is hydrogen, m is zer , W

methoxy or isopropoxy, X^4 is $-(CH_2)_3-$ and R is thiazolyl, imidazolyl, pyrrolyl, oxazolyl or thiadiazolyl.

(6) A compound of the formula Ib wherein R^3 is a group of the formula IX wherein the substituents at positions "2" and "3" of the nitrogen containing ring are in the cis configuration, R^{19} is benzhydryl, r is two and the fused bicyclic ring system to which W and the $-CH_2NR^2R^3$ sidechain are attached is benzisoxazolyl or benzthiazolyl.

(7) A compound of the formula Ib wherein R^3 is a group of the formula IX, R^{19} is benzhydryl, the fused bicyclic ring system to which W and the $-CH_2NR^2R^3$ sidechain are attached is benzisoxazolyl, and W is methoxy.

(8) A compound of the formula Ib wherein R^3 is a group of the formula VII, R^{12} is phenyl, each of R^{13}, R^{14}, R^{15} and R^{16} is hydrogen, m is zero, X^4 is $-(CH_2)_3-$, and the fused bicyclic ring system to which W and the $-CH_2NR^2R^3$ sidechain are attached is benzothiazolyl, benzoxazolyl or benzimidazolyl.

(9) A compound of the formula Ia wherein R^3 is a group of the formula VII, each of R^{13}, R^{14}, R^{15} and R^{16} is hydrogen, m is zero, X^4 is $-(CH_2)_3-$, A is phenyl, W is methoxy, and R is selected from thiazolyl, imidazolyl, thiadiazolyl and isoxazolyl.

(10) A compound of the formula Ia or Ib that is selected from:

(2S,3S)-3-[2-methoxy-5-(2-thiazolyl)benzyl]amino-2-phenylpiperidine;

(2S,3S)-3-[5-(2-imidazolyl)-2-methoxybenzyl]amino-2-phenylpiperidine;

(2S,3S)-3-[2-methoxy-5-(2-oxopyrrolidinyl)benzyl]amino-2-phenylpiperidine;

(2S,3S)-3-[2-methoxy-5-(4-methyl-2-thiazolyl)benzyl]-amino-2-phenylpiperidine;

(2S,3S)-3-[2-methoxy-5-(1,2,3-thiadiazol-4-yl)benzyl]-amino-2-phenylpiperidine;

(2S,3S)-(6-meth xy-2-methyl-benzothiazol-5-ylmethyl)-(2-phenylpiperidin-3-yl)amine;

(2S,3S)-[5-(2,5-dimethyl-pyrrol-1-yl)-2-methoxybenzyl]-(2-phenylpiperidin-3-yl)amine;

(2S,3S)-3-[2-methoxy-5-(5-oxazolyl)benzyl]amino-2-phenylpiperidine;

(2S,3S)-(6-methoxy-2-methyl-benzoxazol-5-ylmethyl)-(2-phenyl-piperidin-3-yl)-amine; and

(1SR,2SR,3SR,4RS)-3-[6-methoxy-3-methylbenzisoxazol-5-yl]methylamino-2-benzhydrylazanorbornane.

(11) A compound of the formula Ic, wherein R^3 is a group of the formula II, III, VII or IX; R^2 is hydrogen; ring AA is phenyl or indolinyl; W^1 is (C_1-C_3)alkoxy optionally substituted with from one to three fluorine atoms; and R^1 is $S(O)_v-(C_1-C_{10})$alkyl wherein v is zero, one or two, $S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, (C_1-C_{10})alkyl-$\underset{|}{N}$-SO_2-(C_1-C_{10})alkyl wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ or (C_1-C_{10})alkyl-$\underset{|}{N}$-SO_2-aryl wherein said aryl is phenyl or benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo.

(12) A compound as defined in paragraph 11 above, wherein R^3 is a group of the formula II, o is two, and each R^6 and R^7 is phenyl.

(13) A compound as defined in paragraph 11 above, wherein R^3 is a group of the formula VII, each of R^{13}, R^{14}, R^{15} and R^{16} is hydrogen, R^{12} is phenyl, m is zero and X^4 is $-(CH_2)_3-$.

(14) A compound as defined in paragraph 11 above, wherein R^3 is a group of the formula IX, R^{19} is benzhydryl and r is two.

(15) A compound as defined in paragraph 11 above, wherein R^3 is a group of the formula III, R^8 is other than hydrogen and R^9 is benzyhydryl.

(16) A compound to the formula Ic wherein the substituents at positions "2" and "3" of the nitrogen containing ring are in the cis configuration.

(17) A compound of the formula 1c wherein R^3 is a group of the formula II wherein the substituents at positions "2" and "3" of the nitrogen containing ring are in the cis configuration, o is two, each of R^6 and R^7 is phenyl and ring AA is phenyl or indolinyl.

(18) A compound of the formula Ic wherein R^3 is a group of the formula III wherein the substituents at positions "2" and "3" of the nitrogen containing ring are in the cis configuration, R^8 is other than hydrogen, R^9 is benzhydryl and ring AA is phenyl.

(19) A compound of the formula Ic wherein R^3 is a group of the formula VII wherein R^{12} and the substituent at position "3" of the nitrogen containing ring are in the cis configuration, ring AA is phenyl, R^{12} is phenyl, each of R^2, R^{13}, R^{14}, R^{15} and R^{16} is hydrogen, m is zero, X^4 is $-(CH_2)_2-$ or $-(CH_2)_3-$ and R^1 is selected from $S(O)_v-(C_1-C_{10})$alkyl wherein v is zero, one or two, and (C_1-C_{10})alkyl-$\underset{|}{N}$-$SO_2-(C_1-C_{10})$alkyl, and di-(C_1-C_6)alkylamino.

(20) A compound as defined in paragraph 19 above, wherein X^4 is $-(CH_2)_2-$ and W^1 is (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms.

(21) A compound as defined in paragraph 19 above, wherein X^4 is $-(CH_2)_3-$ and W^1 is (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms.

(22) A compound of the formula Ic, wherein R^3 is a group of the formula IX wherein the substituents at positions "2" and "3" of the nitrogen containing ring are in the cis configuration, r is two and R^{19} is benzhydryl.

(23) A compound as defined in paragraph 22 above, wherein ring AA is phenyl, W^1 is (C_1-C_5) alkoxy optionally substituted with from one to three fluorine atoms and R^1 is select d from $-S(O)_v-(C_1-C_{10})$alkyl wherein v is zero, one or

two, di-(C_1-C_6)alkylamino and (C_1-C_{10})alkyl-$\underset{|}{N}$-SO_2-(C_1-C_{10})alkyl.

(24) A compound as defined in paragraph 15 above, wherein ring AA is phenyl, W^1 is (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, and R^1 is selected from -S(O)$_v$-(C_1-C_{10})alkyl wherein v is zero, one or two, and (C_1-C_{10})alkyl-$\underset{|}{N}$-SO_2-(C_1-C_{10})alkyl.

(25) A compound as defined in paragraph 15 above, wherein ring AA is phenyl, W^1 is (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, and R^1 is selected from amino, (C_1-C_6)alkylamino or di-(C_1-C_6)alkylamino.

(26) A compound as defined in paragraph 12 above, wherein ring AA is phenyl, W^1 is (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, and R^1 is selected from -S(O)$_v$-(C_1-C_{10})alkyl wherein v is zero, one or two, and (C_1-C_{10})alkyl-$\underset{|}{N}$-SO_2-(C_1-C_{10})alkyl.

(27) A compound as defined in paragraph 12 above, wherein ring AA is phenyl, W^1 is (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, and R^1 is selected from amino, (C_1-C_6)alkylamino or di-(C_1-C_6)alkylamino.

(28) A compound as defined in paragraph 24 above, wherein W^1 is attached at the "2" position of ring AA and R^1 is attached at the "5" position of ring AA, relative to the point of attachment of the NR^2R^3 containing side chain.

(29) A compound as defined in paragraph 25 above, wherein W^1 is attached at the "2" position of ring AA and R^1 is attached at the "5" position of ring AA, relative to the point of attachment of the NR^2R^3 containing side chain.

(30) A compound as defined in paragraph 26 above, wherein W^1 is attached at the "2" position of ring AA and R^1 is attached at the "5" position of ring AA, relative to th point f attachment of the NR^2R^3 containing side chain.

(31) A compound as defined in paragraph 27 above, wherein W^1 is attached at the "2" position of ring AA and R^1 is attached at the "5" position of ring AA, relative to the point of attachment of the NR^2R^3 containing side chain.

(32) A compound as defined in paragraph 13 above, wherein ring AA is phenyl, W^1 is selected from isopropoxy, OCF_3, OCH_3, $OCHF_2$ and OCH_2CF_3, and R^1 is selected from $-S(O)_v-(C_1-C_{10})$alkyl wherein v is zero, one or two, and (C_1-C_{10})alkyl-$N-SO_2-(C_1-C_{10})$alkyl.

(33) A compound selected from the group consisting of:

(2S,3S)-N-(2-methoxy-5-methylsulfonylphenyl)-methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

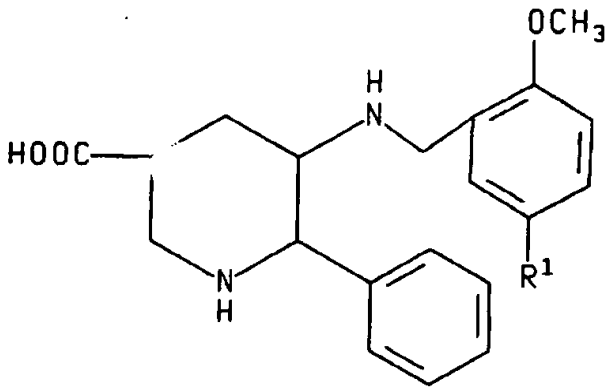
(2S,3S)-N-(2-methoxy-5-methylthiophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(2-methoxy-5-dimethylaminophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine; and

(2S,3S)-N-(5-trifluoroacetylamino-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo-[2.2.2]octan-3-amine.

(34) A compound of the formula Ic, wherein R^1 is a group of the formula VII, m is zero, each of R^{11}, R^{13}, R^{15} and R^{17} is hydrogen, R^{12} is phenyl, R^{14} is $-\overset{O}{\overset{\|}{C}}-OH$, ring AA is phenyl, W^1 is (C_1-C_3)alkoxy and R^1 is selected from (C_1-C_5)alkyl, $-SCH_3$, SO_2CH_3, $SOCH_3$, (C_1-C_6)alkylamino and di-(C_1-C_6)alkyl-amino.

(35) A compound of the formula Ic, having the formula



(36) A compound of the formula Id wherein R^6, R^{10}, R^{11} and R^{13} are phenyl, R^8 is hydrogen, R^9 is phenyl optionally substituted with chlorine, fluorine, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms or (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms, m is 0 and n is 3 or 4.

(37) A compound of the formula Id that is selected from the group consisting of:

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;

(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine;

(2S,3S)-3(-5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

2-(diphenylmethyl)-N-(2-methoxy-5-trifluoromethoxy-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine;

(2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-difluoromethoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine;

(2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxybenzyl)-aminopiperidine; and

(2S,3S)-2-phenyl-3-(2-trifluoromethoxybenzyl)]aminopiperidine.

(38) A compound of the formula Id, wherein R^3 is a group of the formula II wherein o is two or three and each of R^6 and R^7 is phenyl or substituted phenyl.

(39) A compound of the formula Id, wherein R^3 is a group of the formula III, R^8 is hydrogen and R^9 is phenyl or substituted phenyl.

(40) A compound of the formula Id, wherein R^3 is a group of the formula IV wherein l is one or two and each of R^{10} and R^{11} is phenyl or substituted phenyl.

(41) A compound of the formula Id, wherein R^3 is a group of the formula V wherein n is zero or one and each of R^{10} and R^{11} is phenyl or substituted phenyl.

(42) A compound of the formula Id, wherein R^3 is a group of the formula VI wherein p is one and each of R^{10} and R^{11} are phenyl or substituted phenyl.

(43) A compound of the formula Id, wherein R^3 is a group of the formula VII wherein q is two, three or four, m is zero and R^{12} is phenyl or substituted phenyl.

(44) A compound of the formula Id, wherein R^3 is a group of the formula VIII wherein y is zero, x is zero or one, z is three or four, m is zero and R^{12} is phenyl or substituted phenyl.

(45) A compound of the formula Id wherein R^3 is a group of the formula VII, R^6, R^{14}, R^{13} R^{16} and R^{15} are hydrogen, R^{12} is phenyl, X^1 is 2-methoxy, X^2 and X^3 are independently selected from hydrogen, chlorine, fluorine, methyl, (C_1-C_6)alkoxy and trifluoromethan , m is 0 and q is 3 r 4.

(46) A compound of the formula Id wherein R^3 is a group of the formula VII and said compound is selected from the group consisting of:

cis-3-(2-chlorobenzylamino)-2-phenylpiperidine;

cis-3-(2-trifluoromethylbenzylamino)-2-phenylpiperidine;

cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(2-chlorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(2-methylphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-methoxyphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-chlorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(2-methoxybenzylamino)-2-(3-methylphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(4-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-thienyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-phenylazacyclo-heptane;

3-(2-methoxybenzylamino)-4-methyl-2-phenyl-piperidine;

3-(2-methoxybenzylamino)-5-methyl-2-phenyl-piperidine;

3-(2-methoxybenzylamino)-6-methyl-2-phenyl-piperidine;

(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(5-carboethoxypent-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(6-hydroxy-hex-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(4-hydroxy-4-phenylbut-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(4-oxo-4-phenylbut-1-yl)-3-(2-m thoxybenzylamino)-2-phenylpiperidin ;

(2S,3S)-1-(5,6-dihydroxyhex-1-yl)-3-(2-methoxybenzylamin)-2-phenylpiperidine;

cis-3-(5-fluoro-2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-[4-(4-fluorophenyl)-4-oxobut-1-yl]-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-[4-[4-fluorophenyl)-4-hydroxybut-1-yl]-3-(2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(2-methoxy-5-methylbenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(4-benzamidobut-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(2-methoxynaphth-1-ylmethylamino)-2-phenylpiperidine;

(2S,3S)-3-(2-methoxybenzylamino)-1-(5-N-methylcarboxamidopent-1-yl)-2-phenylpiperidine;

(2S,3S)-1-(4-cyanobut-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-[4-(2-naphthamido)but-1-yl]-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(5-benzamidopent-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(5-aminopent-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-3-(5-chloro-2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-3-(2,5-dimethoxybenzylamino)-2-phenylpiperidine;

cis-3-(3,5-difluoro-2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(4,5-difluoro-2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(2,5-dimethoxybenzylamino)-1-[4-(4-fluorophenyl)-4-oxobut-1-yl]-2-phenylpiperidine;

cis-3-(5-chloro-2-methoxybenzylamino)-1-(5,6-dihydroxyhex-1-yl)-2-phenylpiperidine;

cis-1-(5,6-dihydroxyhex-1-yl)-3-(2,5-dimethoxybenzylamino)-2-phenylpiperidine;

cis-2-phenyl-3-[-2(prop-2-yloxy)benzylamino]piperidine;

cis-3-(2,5-dimethoxybenzyl)amino-2-(3-methoxyphenyl)piperidine hydrochloride;

cis-3-(5-chloro-2-methoxybenzyl)amino-2-(3-methoxyphenyl)piperidine dihydrochloride;

cis-3-(5-chloro-2-methoxybenzyl)amino-2-(3-chlorophenyl)piperidine dihydrochloride;

3-(2-methoxybenzylamino)-2,4-diphenylpiperidine;

cis-3-(2-methoxybenzylamino)-2-phenylpyrrolidine;

(2S,3S)-3-(5-ethyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-n-butyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-methoxy-5-n-propylbenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-isopropyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-s-butyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-t-butyl-2-methoxybenzyl)amino-2-phenylpiperidine; and

(2S,3S)-3-(2-methoxy-5-phenylbenzyl)amino-2-phenylpiperidine.

(47) A compound of the formula Id, wherein R^3 is a group of the formula II or III and said compound is selected from the group consisting of:

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-methyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-sec-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine; and

(2S,3S)-N-(5-n-propyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine.

(47A) a compound of the formula Ie that is selected from the group consisting of:

2,4-dimethylthiazole-5-sulfonic acid [4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-methylamide;

N-(4,5-dimethylthiazol-2-yl)-N-[4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-yl-aminomethyl)phenyl]-methanesulfonamide;

{5-[(4,5-dimethylthiazol-2-yl)methylamino]-2-methoxybenzyl}-((2S,3S)-2-phenylpiperidin-3-yl)amine;

{5-(4,5-dimethylthiazol-2-ylamino)-2-methoxybenzyl}-((2S,3S)-2-phenylpiperidin-3-ylamine;

4,5-dimethylthiazole-2-sulfonic acid methyl-[3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)-4-trifluoromethoxyphenyl]-amide;

2,4-dimethylthiazole-5-sulfonic acid [4-isopropoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-methylamide;

2,4-dimethylthiazole-5-sulfonic acid [4-isopropoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-isopropylamide;

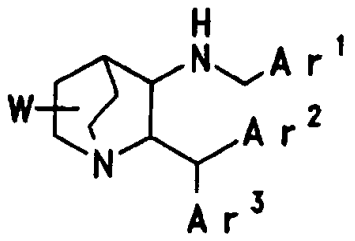
2,4-dimethylthiazole-5-sulfonic acid [4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-isopropylamide;

2,4-dimethylthiazole-5-sulfonic acid [4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-isobutylamide; and

2,4-dimethylthiazole-5-sulfonic acid [4-isopropoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-isobutylamide.

This invention also relates to a method of treating r preventing a disorder of the ye s lected from glaucoma, ocular hypertension, miosis, hyper mia, excess lacrimation

and breakdown of the blood aqueous barrier in a mammal, including a human comprising administering to said mammal an amount of a compound having the formula



(X)

wherein W is Y or $X(CH_2)_n$;

Y is optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl or optionally substituted (C_3-C_8)cycloalkyl;

X is optionally substituted (C_1-C_6)alkoxy, hydroxy, $CONR^1R^2$, CO_2R^1, CHR^1OR^2, $CHR^1NR^2R^3$, COR^1, $CONR^1OR^2$ or optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl; and n is an integer from zero to six;

Ar^1, Ar^2 and Ar^3 are each, independently, optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl;

and R^1, R^2 and R^3 are independently selected from hydrogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl; and optionally substituted (C_1-C_5)heterocyclic groups, wherein said heterocyclic groups are selected from pyrrolidino, piperidino, morpholino, piperazinyl and thiamorpholino;

and wherein the substituents on the foregoing substitut d alkyl, alkenyl, cycloalkyl and alkoxy groups are

independently selected from halo, nitro, amino, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, trifluoromethyl and trifluoromethoxy;

and wherein the substituents on the foregoing substituted (C_1-C_5) heterocyclic groups are attached to a sulfur or nitrogen atom on the ring and are independently selected from oxygen, di-oxygen and (C_1-C_4)alkyl when attached to a ring sulfur atom, and are independently selected from oxygen and (C_1-C_4)alkyl when attached to a ring nitrogen atom;

and wherein the substituents on said substituted Ar^1 groups are independently selected from (C_1-C_6)alkyl optionally substituted with from one to three halo groups, (C_1-C_6)alkoxy optionally substituted with from one to three halo groups, (C_1-C_6)alkylsulfinyl, (C_2-C_6)alkenyl, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, and di-(C_1-C_6)alkylamino wherein one or both of the alkyl groups may be optionally substituted with a (C_1-C_6)alkylsulfonyl, or (C_1-C_6)alkylsulfinyl group;

and wherein the substituents on said substituted Ar^2 and Ar^3 groups are independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl, di-(C_1-C_4)alkylamino, trifluoromethyl and trifluoromethoxy; with the proviso that when Y is unsubstituted or is substituted with (C_1-C_4)alkyl, it is attached to the 4- or 6-position of the quinuclidine ring;

or a pharmaceutically acceptable salt of such compound, that is effective in treating or preventing such disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (48) through (54) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(48) A compound of the formula X, wherein W is $X(CH_2)_n$.

(49) A compound of the formula X, wherein W is Y.

(50) A compound of the formula X, wherein Ar^1 is substituted aryl and W is Y.

(51) A compound of the formula X, wherein Ar^1 is mono-, di- or tri-substituted phenyl and W is Y.

(52) A compound of the formula X, wherein Ar^1 is phenyl disubstituted at the 2- and 5-positions and W is Y.

(53) A compound of the formula X, wherein Ar^1 is paramethoxyphenyl, each of Ar^2 and Ar^3 is phenyl and W is Y.

(54) A compound of the formula X that is selected from the group consisting of:

(3R,4S,5S,6S)-N,N-diethyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-N,N-diethyl-5-(2,5-dimethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-2-methylthiobenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2,5-dimethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo-[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-ethyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxyl-5-n-propylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-sec-butyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-N-methyl-methanesulfonylamino-2-methoxy-benzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfinylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-trifluoromethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfonylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-dimethylamino-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylthiobenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2,5-dimethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(5-ethyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxyl-5-n-propylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(5-sec-butyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(5-N-methylmethanesulfonylamino-2-methoxybenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

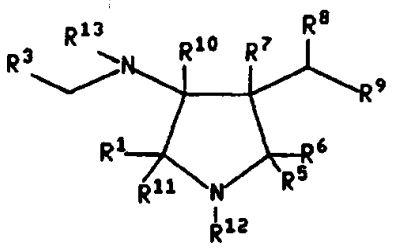
(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfinylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-trifluoromethoxybenzylamino)-6-diphenylm thyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfonylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid; and

(3R,4S,5S,6S)-5-(5-dimethylamino-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma and ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal an amount of a compound having the formula



(XI)

wherein R^1 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine

atoms, (C_1-C_6) alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy),

(C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-

(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-,

(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-,

(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl,

(C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-, -NHCH(=O) and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy optionally substituted with

from one to three fluorine atoms, amino, phenyl, trihaloalkoxy (e.g., trifluoromethoxy),

(C_1-C_6) alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}-$

$-\overset{O}{\overset{\|}{C}}-O-(C_1-C_6)$alkyl, $-\overset{O}{\overset{\|}{C}}H$, $-CH_2OR^{13}$, $NH(C_1-C_6)$alkyl-,

$-NH\overset{O}{\overset{\|}{C}}H$, $-NR^{24}\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl and $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl;

one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, (C_1-C_3)alkyl, (C_1-C_8)acyloxy-(C_1-C_3)alkyl, (C_1-C_8)alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl, $\overset{O}{\overset{\|}{H}}C-$, $R^{14}R^{15}NCO_2CH_2-$, $R^{16}OCO_2CH_2-$, (C_1-C_4)alkyl-CO_2CH_2-, $-CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2-$, $R^{19}OCO_2-$, $C_6H_5CH_2CO_2CH_2-$, $C_6H_5CO_2CH_2-$, (C_1-C_4)alkyl-$CH(OH)-$, $C_6H_5CH(OH)-$, $C_6H_5CH_2CH(OH)-$, CH_2halo, $R^{20}SO_2OCH_2$, $-CO_2R^{16}$ and $R^{21}CO_2-$;

R^{10} and R^{11} are independently selected from hydrogen, (C_1-C_3) alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula

$$R^{22}-\overset{R^{23}}{\underset{|}{(CH_2)_m}}-$$

wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may opti nally be substituted with R^{23};

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

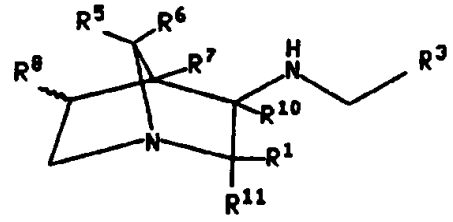
R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)-alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)-alkyl-C(=O)-(C_1-C_6)alkyl, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms,

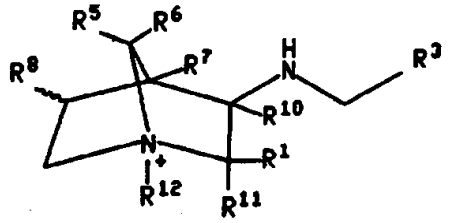
trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHCH(=O) and -NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieti s of said benzhydryl may

optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the proviso that when R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged; or a pharmaceutically acceptable salt of such compound, that is effective in treating or preventing such disorder.

Compounds of the formula XI that contain two pyrrolidine rings may be represented by one of the following two structures, depending on whether R^{12} is present or absent.





Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier and ocular hypertension in a mammal, including a human, that comprise

administering to said mammal an amount of a compound as defined in paragraphs (55) through (59) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(55) A compound of the formula XI wherein R^1 is benzhydryl.

(56) A compound of the formula XI wherein R^1 is diphenylmethyl, R^3 is aryl selected from phenyl or indanyl wherein each of said aryl groups may be optionally substituted with one, two or three substituents, each of R^5, R^6, R^7, R^8, R^{10}, and R^{11} is hydrogen, R^9 is selected from hydroxymethyl, methoxymethyl, $-CO_2R^{16}$, $-CONR^{17}R^{18}$, $R^{14}R^{15}NCO_2CH_2-$, $R^{16}OCO_2CH_2-$, (C_1-C_4)alkyl$-CO_2CH_2-$, $C_6H_5CH_2CO_2CH_2-$, $-CH_2$halo and $R^{20}SO_2OCH_2-$, and R^{12} is hydrogen or benzyl.

(57) A compound of the formula XI wherein R^1 is phenyl, R^3 is aryl selected from phenyl or indanyl wherein each of said aryl groups may be optionally substituted with one, two or three substiuents, each of R^5, R^6, R^7, R^8, R^{10}, and R^{11} is hydrogen, R^9 is selected from hydroxymethyl, methoxymethyl, $-CO_2R^{18}$, $-CONR^{17}R^{18}$, $R^{14}R^{15}NCO_2CH_2CH_2-$, $R^{16}OCO_2CH_2-$, (C_1-C_4) alkyl$-CO_2CH_2-$, $-CH_2$halo, $R^{20}SO_2OCH-$, and R^{12} is hydrogen or benzyl.

(58) A compound of the formula XI wherein R^1 is diphenylmethyl, R^3 is aryl selected from phenyl or indanyl wherein each of said aryl groups may be optionally substituted with one, two or three substituents, each of R^5, R^6, R^7, R^8, R^{10}, R^{11} and R^{13} is hydrogen, and wherein R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen).

(59) A compound of the formula XI that is selected from the group consisting f:

(2S, 3S, 4R)-2-diphenylmethyl-3-[(2-methoxy-4,5-dim thylphenyl)methylamino]-4-(2-hydroxyethyl)pyrr lidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-4,5-dimethylphenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(methylethyl)phenyl)methylamino]-4-(carbomethoxymethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(methylethyl)phenyl)methylamino]-4-(carboxymethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(methylethyl)phenyl)methylamino]-4-(2-dimethylamino-carbamoylethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-trifluoromethoxyphenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2S, 3S, 4R)-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-methoxyethyl)-pyrrolidine;

(2S, 3S, 4R)-2-diphenylmethyl-3-[(2-methoxy-5-methylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-methylethyl)phenyl)methylamino]-4-(2-methoxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methyl-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-4,5-dimethylphenyl)-methylamino]-bicyclo[2.2.1]-heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxyphenyl)methylamino]bicyclo[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]bicyclo-[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]bicyclo-[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1-methylethyl)phenyl)methylamino]bicyclo-[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-propylphenyl)methylamino]bicyclo[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1-methylpropyl)phenyl)methylamino]bicyclo-[2.2.1]heptane;

(1SR, 2SR, 3SR, 4RS)-1-aza-2-phenyl-3-[(2-methoxyphenyl)methylamino]bicyclo[2.2.1]heptane;

(1SR, 2SR, 3RS, 4RS)-1-aza-2-phenyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]bicyclo[2.2.1]heptane;

(2SR, 3SR, 4RS)-N-1-phenylmethyl-2-diphenylmethyl-3-[(2-methoxyphenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-phenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1-methylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)-pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-propylphenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-(1-methyl-1-propyl)phenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-trifluoromethoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

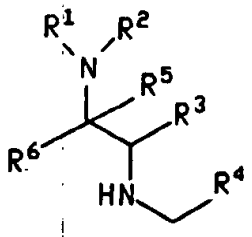
(2SR, 3SR, 4RS)-2-diphenylmethyl-3-[(2-methoxy-5-chlorophenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-phenyl-3-[(2-methoxyphenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine;

(2SR, 3SR, 4RS)-2-phenyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine; and

(2SR, 3SR, 4RS)-2-phenyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]-4-(2-hydroxyethyl)pyrrolidine.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula

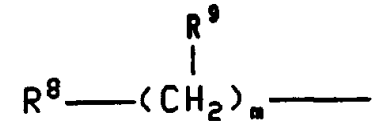


XII

wherein R^1 is hydrogen, (C_1-C_6) alkyl, a saturated (C_6-C_{10}) carbocyclic ring system containing two fused rings, a saturated (C_6-C_{10}) carbocyclic bridged ring system containing two rings, or benzyl wherein the phenyl moiety of said benzyl may optionally be substituted with one or more substituents independently selected from halo, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms

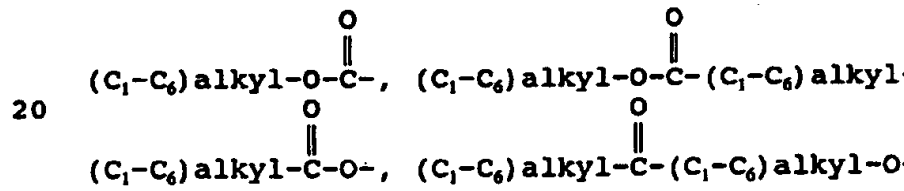
and (C_1-C_8) alkoxy optionally substituted with from one to three fluorine atoms;

R^2 is hydrogen, benzyl or a group of the formula

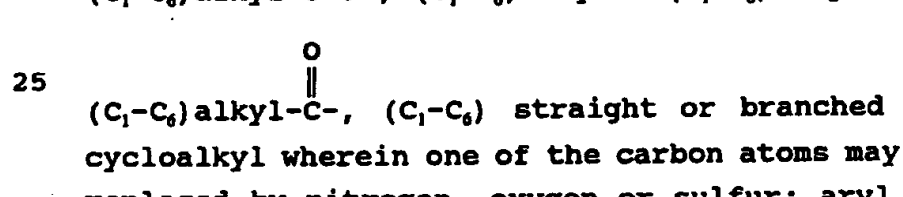


wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^9;

R^8 and R^9 are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy,



(C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl-O-,



(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-,

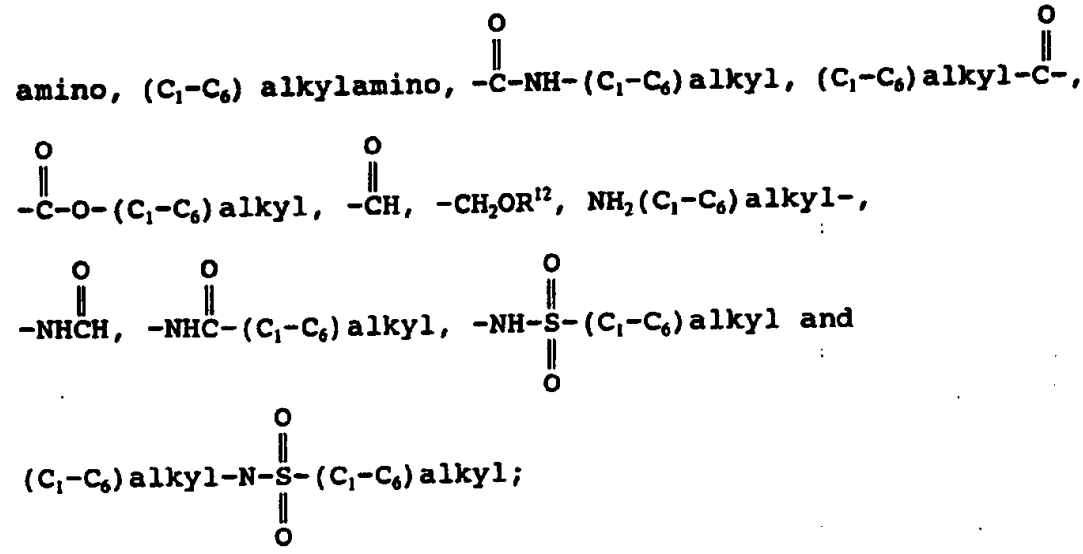
(C_1-C_6)alkyl-C(=O)-, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms,

trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHCH(=O) and -NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a saturated or unsaturated monocyclic ring containing from three to eight carbon atoms, a fused bicyclic ring containing from six to ten carbon atoms, or a saturated bridged ring system containing from six to ten carbon atoms;

R^4 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having from three to seven carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one, two or three substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine

atoms, (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms, phenyl,



amino, (C_1-C_6) alkylamino, $-C-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl$-C-$,

$-C-O-(C_1-C_6)$alkyl, $-CH$, $-CH_2OR^{12}$, $NH_2(C_1-C_6)$alkyl$-$,

$-NHCH$, $-NHC-(C_1-C_6)$alkyl, $-NH-S-(C_1-C_6)$alkyl and

(C_1-C_6)alkyl$-N-S-(C_1-C_6)$alkyl;

R^3 is hydrogen, (C_3-C_8)cycloalkyl, (C_1-C_6) straight or branched alkyl or phenyl optionally substituted with one or more substituents independently selected from halo, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, and (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

R^5 is hydrogen, (C_1-C_6)alkyl, or phenyl optionally substituted with one or more substituents independently selected from halo, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

R^6 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetraz lyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and h teroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected fr m halo, nitro, (C_1-C_6)

alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, trifluoromethyl, amino, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-, -NHCH and -NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl; and

R^{12} is hydrogen, (C_1-C_3)alkyl or phenyl;

or a pharmaceutically acceptable salt of such compound, that is effective in treating or preventing such disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (60) through (62) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(60) A compound of the formula XII wherein R^2 is hydrogen, or R^2 and R^1, together with the nitrogen to which they are attached, form a monocyclic ring containing five to seven carbon atoms; R^3 is hydrogen, methyl or phenyl; R^5 is hydrogen; R^4 is phenyl or indanyl, wherein said phenyl or indanyl may optionally be substituted with from one to three

substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6) alkylamino, -C(O)NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(O)-, -C(O)-O-(C_1-C_6)alkyl, -C(O)H, $-CH_2OR^{12}$, -NH(C_1-C_6)alkyl, -NHC(O)H, -NHC(O)-(C_1-C_6)alkyl, $-NHSO_2$(C_1-C_6)alkyl and (C_1-C_6)alkyl-N-SO_2-(C_1-C_6)alkyl; and R^6 is phenyl.

(61) A compound of the formula XII wherein R^1 is alkyl, R^6 is unsubstituted phenyl, R^4 is a monosubstituted or disubstituted aryl group that is substituted at the C-2 position with an alkoxy group or substituted at the C-5 position with an alkyl, alkoxy or trihaloalkoxy group, or substituted in such manner at both C-2 and C-5 positions (i.e., with an alkoxy group at the C-2 position and an alkyl, alkoxy or trihaloalkoxy group at the C-5 position), and each of R^2, R^3 and R^5 is hydrogen.

(62) A compound of the formula XII that is selected from the group consisting of:

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-trifluoromethoxyphenyl)methyl]-1,2-ethanediamine;

1-N-pyrrolidyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-methyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-propyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-phenylmethyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclooctyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cycl butyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-(2-adamantyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-(1,1-dimethylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-isopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-(1-phenylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-(2-norbornyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

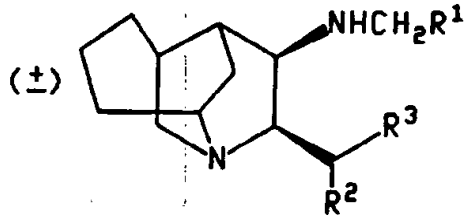
1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-tert-butylphenyl)methyl]-1,2-ethanediamine;

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-isopropylphenyl)methyl]-1,2-ethanediamine;

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-4,5-dimethylphenyl)methyl]-1,2-ethanediamine; and

1-N-cyclohexyl-1-N-(6-hydroxyhexyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula



XIII

wherein R^1 is cycloalkyl having from five to seven carbon atoms, pyrrolyl, thienyl, pyridyl, phenyl or substituted phenyl, wherein said substituted phenyl is substitut d with from ne to three substituents independently selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having

from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety and benzyloxycarbonyl;

R^2 is furyl, thienyl, pyridyl, indolyl, biphenyl, phenyl or substituted phenyl, wherein said substituted phenyl is substituted with one or two substituents independently selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety and benzyloxycarbonyl; and

R^3 is thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl, or a pharmaceutically acceptable salt of such compound, that is effective in treating or preventing such disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (63) through (65) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

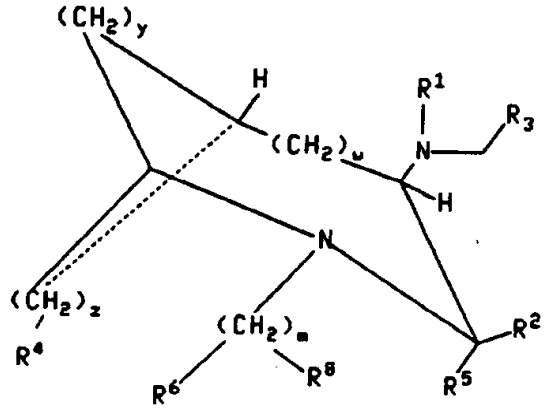
(63) A compound of the formula XIII, wherein R^1 is phenyl or substituted phenyl.

(64) A compound of the formula XIII, wherein R^1 is methoxyphenyl.

(65) A compound of the formula XIII, wherein said compound is (±)-cis-9-diphenylmethyl-N-((2-methoxyphenyl)methyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine.

This invention also relates to a method of treating or preventing a disorder of the ye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown f the bl od aqueous barrier in a mammal,

including a human, comprising administering to said mammal an amount of a compound of the formula



XIV

wherein m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

w is an integer from 0 to 2;

y is an integer from 1 to 4;

z is an integer from 1 to 4, and wherein any one of the carbon atoms of said $(CH_2)_z$ may optionally be substituted with R^4;

R^1 is hydrogen or (C_1-C_8) alkyl optionally substituted with hydroxy, alkoxy or fluoro;

R^2 is a group selected from hydrogen, (C_1-C_6)straight or branched alkyl, (C_3-C_7)cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, indanyl, and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl(C_2-C_6)alkyl, benzhydryl and benzyl, wherein one of the phenyl moieti s of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or

pyridyl and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)- (C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)- (C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)- (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl;

R^5 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^3 is aryl selected from phenyl, indanyl, and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to thre fluorine atoms, trifluoromethyl, phenyl,

amino, (C_1-C_6)alkylamino, (C_1-C_6)dialkyl amino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, $-NH\overset{O}{\overset{\|}{C}}H$ and $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl;

R^4 is independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl$-O-\overset{O}{\overset{\|}{C}}-$, (C_1-C_6)alkyl$-O-\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-O-$, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl$-O-$, hydroxy-$(C_1-C_6)$alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-$, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl-, and the groups set forth in the definition of R^2;

R^6 is $NH\overset{O}{\overset{\|}{C}}R^9$, $NHCH_2R^9$, $NHSO_2R^9$ or one of the groups set forth in any of the definitions of R^2, and R^4;

R^8 is oximino (=NOH) or one of the groups set forth in any of the definitions of R^2, and R^4;

R^9 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

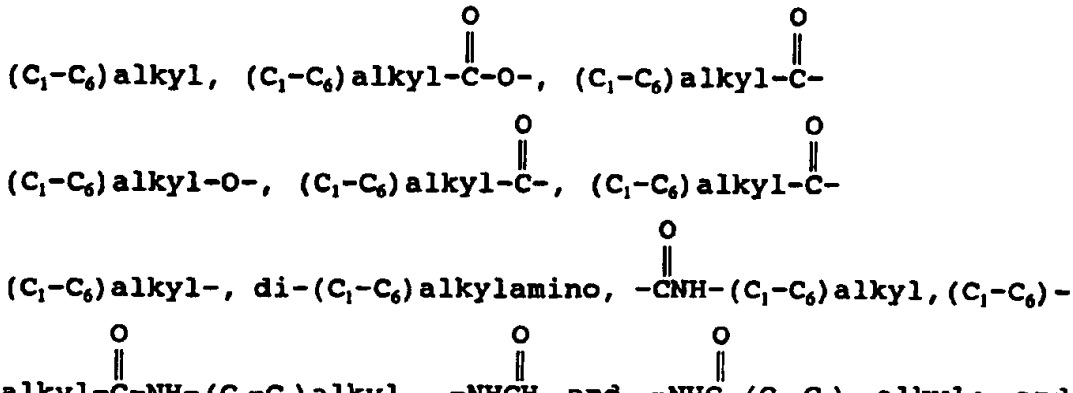
with the proviso that (a) when m is 0, R^8 is absent and R^6 is hydrogen, (b) neither R^4, R^6, nor R^8 can form, together with the carbon to which it is attached, a ring with R^5, (c) the sum of y and z must be less than 7; or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

Preferr d embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia,

excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (66) through (68) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(66) A compound of the formula XIV, wherein R^2 is a radical selected from hydrogen, phenyl, naphthyl and benzhydryl; wherein each of said phenyl, naphthyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6)alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH(=O)-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHCH(=O) and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl.

(67) A compound of the formula XIV, wherein R^2 is a group selected from hydrogen, phenyl, naphthyl and benzhydryl; wherein each of said phenyl, naphthyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-



(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-

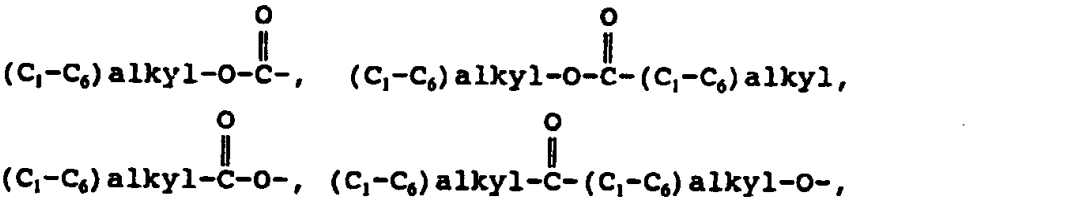
(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-

(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-

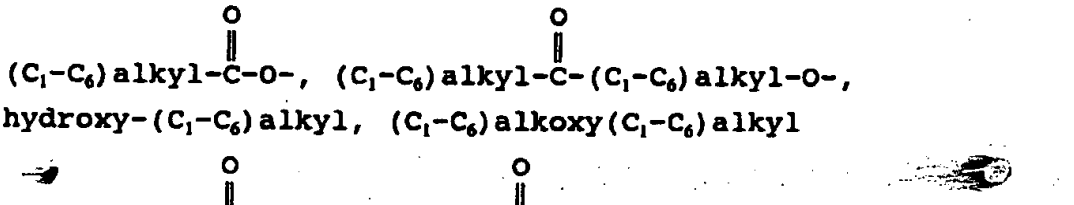
alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHCH(=O) and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl; and

R^4 is independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile,

(C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy,

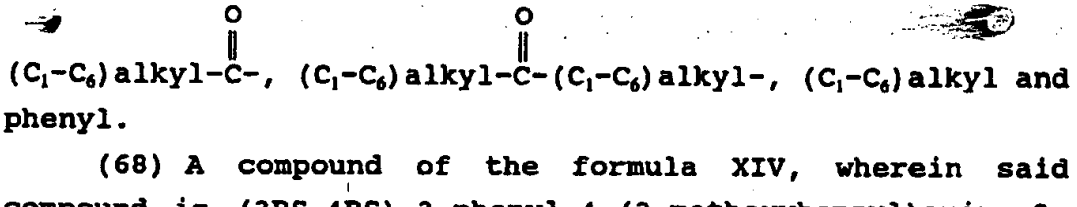


(C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,



(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-,

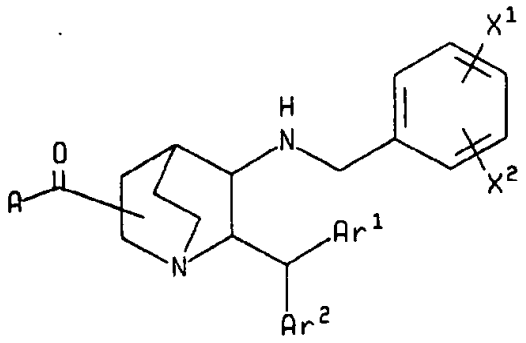
hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl



(C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, (C_1-C_6)alkyl and phenyl.

(68) A compound of the formula XIV, wherein said compound is (3RS,4RS)-3-phenyl-4-(2-methoxybenzyl)amino-2-azabicyclo[3.3.1]nonane.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma and ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal a compound of the formula



XV

wherein X^1 is C_1-C_5 alkoxy or halosubstituted (C_1-C_5) alkoxy;

X^2 is hydrogen, halogen, (C_1-C_5)alkyl, (C_2-C_5)alkenyl, (C_2-C_5)alkynyl, (C_1-C_5)alkoxy, (C_1-C_5)alkylthio, (C_1-C_5) alkylsulfinyl, (C_1-C_5) alkylsulfonyl, halosubstituted (C_1-C_5) alkyl, halosubstituted (C_1-C_5) alkoxy, (C_1-C_5)alkylamino, dialkylamino having from 1 to 5 carbon atoms in each alkyl moiety, (C_1-C_5)alkylsulfonylamino (which may be substituted by halogen), (C_1-C_5)alkyl-N-(C_1-C_5)alkylsulfonyl (which may be substituted by halogen in the alkylsulfonyl moiety), (C_1-C_5)alkanoylamino (which may be substituted by halogen) or (C_1-C_5)alkyl-N-(C_1-C_5)alkanoyl (which may be substituted by halogen in the alkanoyl moiety);

Ar^1 and Ar_2 are each, independently, thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;

A is $Y-(CH_2)_m-CH(R^2)-(CH_2)_n-NR^1-$;

R^1 is hydrogen, (C_1-C_5)alkyl, benzyl or $-(CH_2)_p-Y$;

R^2 is hydrogen, (C_1-C_5)alkyl (which may be substituted by a substituent selected from the group consisting of hydroxy, amino, methylthio and mercapto), benzyl, 4-hydroxybenzyl, 3-indolylmethyl or $-(CH_2)_p-Y$;

Y is -CN, $-CH_2Z$ or -COZ;

Z is hydroxy, amino, (C_1-C_5)alkoxy, (C_1-C_5) alkylamino or dialkylamino having from 1 to 5 carbon atoms in each alkyl moiety;

m, n and p are each, independently, 0, 1, 2 or 3; and

R^1 and R^2 may be connected to form a ring;

or a pharmaceutically acceptable salt of such compound, that is effective in treating or preventing such disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraph (69) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(69) A compound of the formula XV, wherein said compound is selected from the group consisting of:

(3R,4S,5S,6S)-N-carbamoylmethyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-N-carboxymethyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

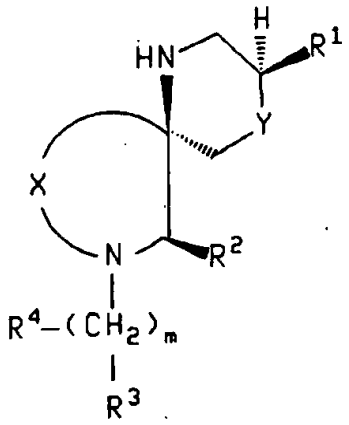
(3R,4S,5S,6S)-3-(2-carbamoylpyrrolidin-1-yl)carbonyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane;

(3R*,4S*,5S*,6S*)-N-(1-carbamoylethyl)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-N-(1-carbamoyl-3-methylbutyl)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octan -3-carboxamide; and

(3R,4S,5S,6S)-N-(2-carbamoylethyl)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula

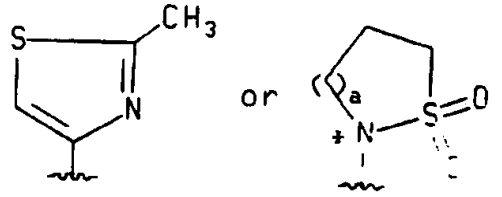


XVI

wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$ alkyl, hydroxy(C_1-C_4)alkyl, $-\overset{O}{\overset{\|}{NHCH}}$, $-\overset{O}{\overset{\|}{NHC}}-(C_1-C_6)$ alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-S(O)_v-(C_1-C_{10})$-alkyl wherein v is zero, one or two, $-S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, $-SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5,

together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, (C_1-C_{10})alkyl-$\overset{|}{N}$-SO_2-(C_1-C_{10})alkyl wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and (C_1-C_{10})alkyl-$\overset{|}{N}$-SO_2-aryl; and wherein the aryl moieties of said $-S(O)_v$-aryl, -O-aryl and (C_1-C_{10})alkyl-$\overset{|}{N}$-SO_2-aryl are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;

or R^1 is phenyl substituted with a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R;

R^2 is selected from (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three

fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino,

(C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl,

(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-,

(C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-,

di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl,

(C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;

R^3 is selected from $NHCR^8$, $NHCH_2R^8$, SO_2R^8, AR^9, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;

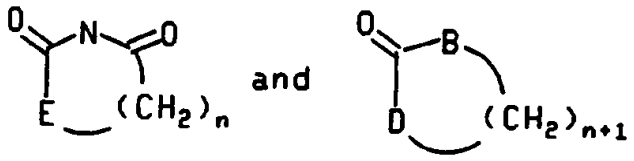
A is CH_2, nitrogen, oxygen, sulfur or carbonyl;

R^8 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

R^4 is selected from oximino (=NOH) and the radicals set forth in the definitions of R^2, R^6 and R^7;

R^9 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl,

2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



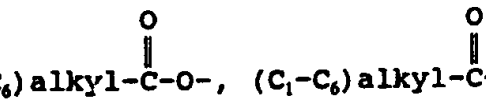
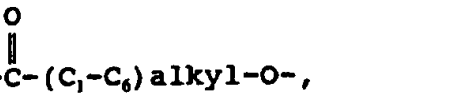
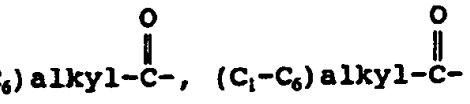
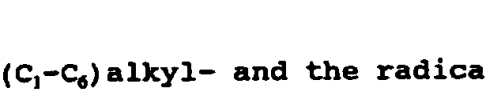
wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;

R^6 and R^7 are independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino,

di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, $-C(=O)-OH$,

(C_1-C_6)alkyl-$O-C(=O)-$, (C_1-C_6)alkyl-$O-C(=O)-(C_1-C_6)$alkyl,

(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl- and the radicals set forth in the definition of R^2; and

Y is $(CH_2)_z$ wherein z is zero or one;

with the proviso that: (a) when A is $-(CH_2)-$ or carbonyl, R^9 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; and (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom;

or a pharmaceutically acceptable salt of such compound, that is effective in treating or preventing such disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraph (70)-(75) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(70) A compound of the formula XVI wherein z is one.

(71) A compound of the formula XVI wherein q is three.

(72) A compound of the formula XVI wherein q is three, m is zero, R^3 is hydrogen and R^4 is absent.

(73) A compound of the formula XVI wherein R^1 is phenyl substituted with from one to three substituents independently selected from (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6)alkoxy optionally substituted with from one to three flourine atoms.

(74) A compound of the formula XVI wherein z is one, m is zero, R^4 is absent, and each of R^3, R^6 and R^7 is hydrogen.

(75) A compound of the formula XVI that is selected from the group consisting of:

(±)-[3R-[3α, 6α (R*)]]-3-phenyl-7-phenyl-1,8-diazaspiro[5.5]undecane; and

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane.

Other compounds of the formula I include the following:

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxy-5-trifluoromethoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(5-chloro-2-methoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(5-isopropyl-2-methoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(5-tert.butyl-2-methoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxy-5-(N-methyl-N-methylsulfonylaminophenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-iodophenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-methoxy-4-methylphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-isopropoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α, 6α (R*)]]-3-(2-difluoromethoxy-5-trifluoromethoxyphenyl)-7-phenyl-1,8-diazaspiro[5.5]undecane;

(±)-[3R-[3α 5α (R*)]]-3-(2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane;

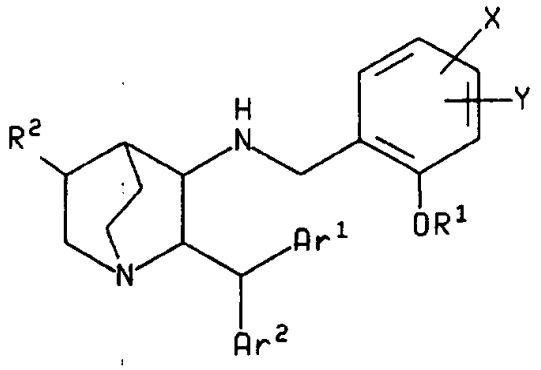
(±)-[3R-[3α, 5α (R*)]]-3-(2-methoxy-5-trifluoromethoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane;

(±)-[3R-[3α, 5α (R*)]]-3-(5-chloro-2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane;

(±)-[3R-[3α, 5α (R*)]]-3-(5-isopropyl-2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane; and

(±)-[3R-[3α, 5α (R*)]]-3-(5-tert.butyl-2-methoxyphenyl)-6-phenyl-1,7-diazaspiro[4.5]decane.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula



XVII

wherein Ar^1 and Ar^2 are each independently aryl or substituted aryl;

R^1 is alkyl having from 1 to 6 carbon atoms;

R^2 is hydrogen or alkyl having from 1 to 6 carbon atoms;

and either X and Y are taken separately and they are each, independently, hydrogen, dialkylphosphoryl having from 2 to 12 carbon atoms, alkyl having from 1 to 6 carbon atoms; or X and Y are taken together and they represent a hydrocarbon chain having 3, 4, or 5 carbon atoms, optionally containing up to 2 double bonds and optionally having 1 or 2 substituents selected from oxo, hydroxy and alkyl having from 1 to 6 carbon atoms;

provided that when X and Y are taken together they are attached to adjacent carbon at ms; and

provided that if either X or Y is hydrogen, then the other one must be alkenyl or alkynyl;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

The term "alkylthio" is used in formula XVII to mean $-SR^4$ (R^4 is alkyl) including, but not limited to, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, t-butylthio and the like.

The term "dialkylphosphoryl" is used in formula XVII to mean $-P(O)(OR^5)(OR^6)$ (R^5 and R^6 are alkyl) including, but not limited to, diethylphosphoryl, ethylmethylphosphoryl and the like.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (76) - (79) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(76) Compounds of formula XVII wherein Ar^1 and Ar^2 are each phenyl, R^1 is methyl, R^2 is hydrogen, X is alkenyl or alkynyl and Y is hydrogen.

(77) Compounds of the formula XVII wherein Ar^1 and Ar^2 are each phenyl, R^1 is methyl, R^2 is hydrogen and X and Y are each alkyl.

(78) Compounds of the formula XVII wherein Ar^1 and Ar^2 are each phenyl, R^1 is methyl, R^2 is hydrogen and X and Y represent $CH_2CH_2CH_2$ or $CH_2CH_2CH_2CH_2$.

(79) A compound of the formula XVII that is selected from:

(2S,3S)-N-(5-Isopropenyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(2-Methoxy-5-vinylphenyl)methyl-2-diphenylm thyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(2-Methoxy-4,5-dimethylphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

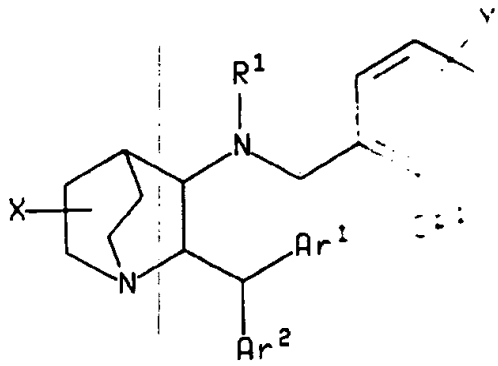
(2S,3S)-N-(5,6,7,8-Tetrahydro-3-methoxy-2-naphthyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-Methoxyindan-6-yl)methyl-6-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-3-(2,4-Dimethoxy-5-ethylbenzylamino)-2-diphenylmethyl-1-azabicyclo[2.2.2.]octane; and

(2S,3S)-2-Diphenylmethyl-N-[2-methoxy-5-(diethylphosphoryl)phenyl]methyl-1-azabicyclo[2.2.2]octan-3-amine.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula



XVIII

wherein Ar^1 and Ar^2 are each, independently, thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;

X is $-CONR^3R^4$, $-CO_2R^3$, $-CH_2OR^3$, $-CH_2NR^3R^4$ or $-CONR^3OR^4$;

R^1, R^3 and R^4 are each, independently, hydrogen or alkyl having 1 to 4 carb n atoms;

R^2 is alkyl having 1 to 4 carbon atoms;

Y is alkylsulfonyl having 1 to 4 carbon atoms, N-alkyl-N-alkanoylamino (which may be substituted by halogen in the alkanoyl moiety) having 1 to 4 carbon atoms in the alkyl and the alkanoyl moieties, N-alkyl-N-alkylsulfonylamino (which may be substituted by halogen in the alkylsulfonyl moiety) having 1 to 4 carbon atoms in the alkyl and the alkyl sulfonyl moieties, alkenyl having 2 to 4 carbon atoms, alkynyl having 2 to 4 carbon atoms, halosubstituted alkyl having 1 to 4 carbon atoms, alkylamino having 1 to 4 carbon atoms, alkanoylamino (which may be substituted by halogen) having 1 to 4 carbon atoms or alkylsulfonylamino (which may be substituted by halogen) having 1 to 4 carbon atoms;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (80) - (86) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(80) A compound of the formula XVIII wherein Ar^1 and Ar^2 are each phenyl.

(81) A compound as described in paragraph (80) wherein R^2 is methyl and R^1 is hydrogen.

(82) A compound as described in paragraph (81) wherein X is at the 3-position of the quinuclidine ring and X is carboxy or aminocarbonyl.

(83) A compound as described in paragraph (82) wherein Y is said alkenyl.

(84) A compound as described in paragraph (83) wherein Y is isopropenyl.

(85) A compound as described in paragraph (82) wherein Y is methylsulfonyl, N-acetyl-N-methylamino or N-methyl-N-methylsulfonylamino.

(86) A compound of the formula XVIII that is selected from:

(3R,4S,5S,6S)-5-(5-Isopropenyl-2-methoxybenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

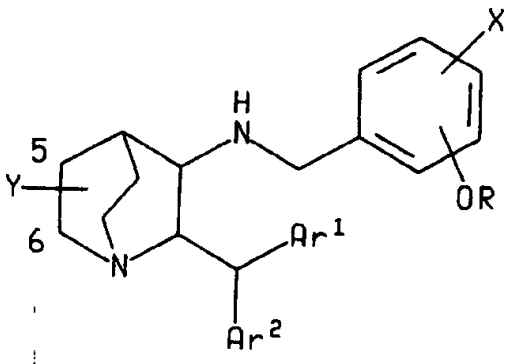
(3R,4S,5S,6S)-6-Diphenylmethyl-5-(2-methoxy-5-methylsulfonylbenzylamino)-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-5-[5-(N-Acetyl-N-methylamino)-2-methoxybenzylamino]-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-6-Diphenylmethyl-5-[2-methoxy-5-(N-methyl-N-methylsulfonylamino)benzylamino]-1-azabicyclo[2.2.2]octane-3-carboxamide; and

(3R,4S,5S,6S)-6-Diphenylmethyl-5-(2-methoxy-5-methylsulfonylbenzylamino)-1-azabicyclo[2.2.2]octane-3-carboxylic acid.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal a compound of the formula



XIX

wherein R is C_1-C_6 alkyl;

X is C_1-C_6 alkyl having one or more substituents bonded through a heteroatom;

Ar^1 and Ar^2 are each, independently, aryl optionally substituted by one C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, cyano, nitro, phenoxy, mono C_1-C_6 alkylamino, di C_1-C_6 alkylamino, halosubstituted C_1-C_6 alkyl, or halosubstituted C_1-C_6 alkoxy;

Y is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, $Z-(CH_2)_p-$, or $W-(CH_2)_m-CHR^2-(CH_2)_n-NR^1CO-$ wherein Y is at the 4-, 5- or 6-position on the quinuclidine ring;

R^1 is hydrogen, C_1-C_6 alkyl, benzyl or $-(CH_2)_r-W$;

R^2 is hydrogen or C_1-C_6 alkyl which may be substituted by one hydroxy, amino, methylthio, mercapto, benzyl, 4-hydroxybenzyl, 3-indolylmethyl or $-(CH_2)_r-W$;

Z is C_1-C_6 alkoxy, $-CONR^4R^5$, $-CO_2R^4$, $-CHR^4OR^5$, $-CHR^4NR^5R^6$, $-COR^4$, $-CONR^4OR^5$ or optionally substituted aryl;

each W is independently cyano, hydroxymethyl, C_2-C_6 alkoxymethyl, aminomethyl, mono C_1-C_6 alkylaminomethyl, di C_1-C_6 alkylaminomethyl, carboxyl, carbamoyl or C_1-C_6 alkoxycarbonyl;

R^4, R^5 and R^6 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl or an optionally substituted aryl or heterocyclic group;

p is 0 to 6; and

m, n and r are each, independently, 0 to 3;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraphs (87) - (91) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(87) A compound of the formula XIX wherein X is C_1-C_6 alkyl having one or two substituents selected from hydroxy, halogen, C_1-C_6 alkoxy, C_2-C_6 alkanoyl, C_2-C_6 alkanoyloxy, C_1-C_6 alkylthio, mono C_1-C_6 alkylamino, di C_1-C_6 alkylamino, amino, cyano and azido.

(88) A compound of the formula XIX as described in paragraph (87) wherein R is methyl and the OR group is at the 2-position; Ar^1 and Ar^2 are each phenyl, monochlorophenyl or monofluorophenyl; Y is hydrogen or $Z-(CH_2)_p-$, wherein Z is C_1-C_6 alkoxy, $-CONR^4R^5$, $-CO_2R^4$, $-CHR^4OR^5$, $-CHR^4NR^5R^6$, $-COR^4$ or $-CONR^4OR^5$; and Y is at the 5- or 6-position.

(89) A compound as described in paragraph (88) wherein X is C_1-C_6 alkyl having one or two substituents selected from hydroxy, C_1-C_6 alkoxy and C_1-C_6 alkylthio; Ar^1 and Ar^2 are each phenyl; and Y is hydrogen or carboxy.

(90) A compound is described in paragraph (89) wherein X is $-C(CH_3)_2OH$, $-C(OH)(CH_3)CH_2OH$, $-C(CH_3)_2OCH_3$ or $-C(CH_3)_2SCH_2CH_3$.

(91) A compound as described in paragraph (90) that is selected from:

(2S,3S)-N-[5-(1-hydroxy-1-methylethyl)-2-methoxy-phenyl]methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-[2-methoxy-5-(1-methoxy-1-methylethyl)-phenyl]methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(3R,4S,5S,6S)-3-[5-(1-hydroxy-1-methylethyl)-2-methoxyphenyl]methylamino-6-diphenylmethyl-1-azabicyclo[2.2.2]octan-5-carboxylic acid;

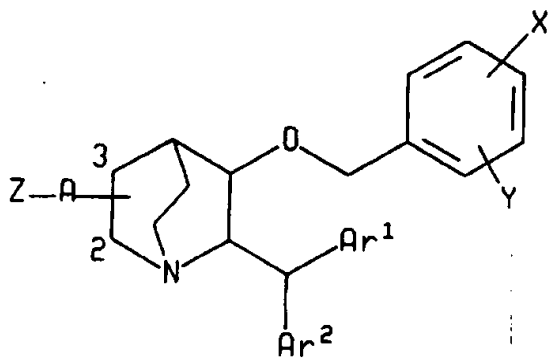
(2S,3S)-2-diphenylmethyl-N-[5-(1-hydroxy-1-hydroxymethylethyl)-2-methoxyphenyl]methyl-1-azabicyclo[2.2.2]octan-3-amine;

(3R,4S,5S,6S)-3-[5-(1-methoxy-1-methylethyl)-2-methoxyphenyl]methylamino-6-diphenylmethyl-1-azabicyclo[2.2.2]octan-5-carboxylic acid;

(3R,4S,5S,6S)-3-[5-(1-hydroxy-1-methylethyl)-2-methoxyphenyl]methylamino-6-diphenylmethyl-1-azabicyclo[2.2.2]octan-5-carboxylic acid; and

(3R,4S,5S,6S)-3-[5-(1-ethylthio-1-methylethyl)-2-methoxyphenyl]methylamino-6-diphenylmethyl-1-azabicyclo[2.2.2]octan-5-carboxylic acid.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal a compound of the formula



XX

wherein X and Y are each hydrogen, halo, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl or tri C_1-C_6 alkylsilyl;

Ar^1 and Ar^2 are each aryl optionally substituted by halo;

A is -CO- or $-(CH_2)-$;

Z-A- is at the 2 or 3 position on the quinuclidine ring;

Z is hydroxy, C_1-C_6 alkoxy, NR^1R^2 or $W^1-(CH_2)_m-CHR^4-(CH_2)_n-NR^3$ wherein

R^1 and R^2, when taken separately, are each hydrogen or C_1-C_6 alkyl;

R^1 and R^2, when taken together with the nitrogen atom to which they are attached, represent piperidino, pyrrolidino, morpholino, thiomorpholino or piperazino;

R^3 is hydrogen, C_1-C_6 alkyl, benzyl or $-(CH_2)_r-W^2$;

R^4 is hydrogen or C_1-C_6 alkyl which may be substituted by hydroxy, amino, methylthio, mercapto, benzyl, 4-hydroxylbenzyl, 3-indolylmethyl or $-(CH_2)_s-W^3$;

R^3 and R^4, when taken together, represent CH_2 or CH_2CH_2;

W^1, W^2 and W^3 are each cyano, hydroxymethyl, C_2-C_6 alkoxymethyl, aminomethyl, (C_1-C_6 alkylamino)methyl, (di C_1-C_6 alkylamino)methyl, carboxyl, (C_1-C_6 alkyl)carbamoyl, or (di C_1-C_6 alkyl)carbamoyl, carbamoyl or (C_1-C_6 alkoxy)carbonyl; and

m, n, r and s are each 0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof that is effective in treating or preventing such disorder.

As used in formula XX, the term "alkylthio" means -S-alkyl, including but not limited to methylsulfinyl, ethylsulfinyl, isopropylsulfinyl and the like;

As used in formula XX, the term "alkylsulfonyl" means $-SO_2$-alkyl including but not limited to methylsulfonyl, ethylsulfonyl, isopropylsulfonyl and the like; and

As used in formula XX, the term "aryl" means aromatic radicals including but not limited to phenyl, naphthyl,

pyridyl, quinolyl, thienyl, furyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl, pyrazolyl and the like. These aryl groups can be substituted by C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, cyano, nitro, phenoxy, mono- or di-C_1-C_6 alkylamino and the like.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, that comprise administering to said mammal an amount of a compound as defined in paragraph (92) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(92) A compound of the formula XX that is selected from the group consisting of:

(3S,4R,5S,6S)-N-carbamoylmethyl-6-diphenylmethyl-5-(3,5-bis(trifluoromethyl)benzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3S,4R,5S,6S)-6-diphenylmethyl-5-(3,5-bis(trifluoromethyl)benzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3S,4R,5S,6S)-N,N-(3-oxa-1,5-pentylene)-6-diphenylmethyl-5-(3,5-bis(trifluoromethyl)benzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3S,4R,5S,6S)-6-diphenylmethyl-5-(3,5-dimethylbenzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

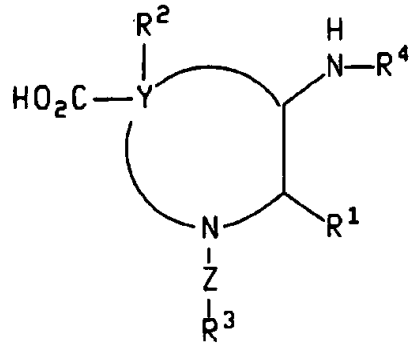
(3S,4R,5S,6S)-N,N-diethyl-6-diphenylmethyl-5-(3,5-bis(trifluoromethyl)benzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3S,4R,5S,6S)-6-diphenylmethyl-5-(3-fluoro-5-triflu romethylbenzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3S,4R,5S,6S)-6-diphenylmethyl-5-(3,5-bis(trifluoromethyl)benzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxylic acid; and

(3S,4R,5S,6S)-N,N-dimethyl-6-diphenylmethyl-5-(3,5-bis(trifluoromethyl)benzyloxy)-1-azabicyclo[2.2.2]octane-3-carboxamide.

This invention also relates to a method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, including a human, comprising administering to said mammal a compound of the formula



XXI

wherein Y is C_2-C_4 alkylene;

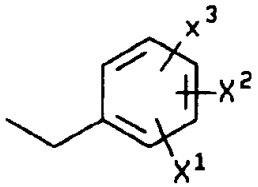
Z is a valence bond or C_1-C_6 alkylene;

R^1 is phenyl, biphenyl, indanyl, naphthyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, tetrazolyl, quinolyl, phenyl C_1-C_6 alkyl- or benzhydryl, wherein each of the ring moieties may optionally be substituted by one or more substituents independently selected from halogen, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkyl, C_1-C_6 alkoxy and halosubstituted C_1-C_6 alkoxy;

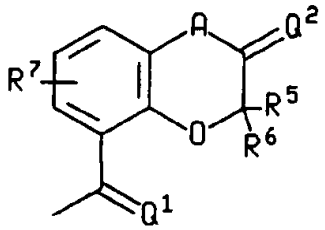
R^2 is hydrogen or C_1-C_6 alkyl;

R^3 is hydrogen, hydr xy, cyano, amino or carboxy; and

R^4 represents a group of the formula (II) r (III)



II



III

wherein X^1, X^2 and X^3 are each halo, hydrogen, nitro, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkoxy, halosubstituted C_1-C_6 alkoxy, hydroxy, amino, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl or C_1-C_6 alkylsulfonyl;

Q^1 and Q^2 are each H_2, oxygen or sulfur;

A is valence bond, methylene, oxygen, sulfur or NH;

R^5 and R^6 are each hydrogen or C_1-C_6 alkyl; and

R^6 is hydrogen, halogen, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkyl or C_1-C_6 alkoxy;

provided that when Z is a valence bond, R^3 must be hydrogen;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

Preferred embodiments of this invention include methods of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation nd breakdown of the blood aqueous barrier in a mamma., including a human, that comprise administering to said mammal an amount of a compound as defined in paragraph (93) below, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

(93) A compound of the form XXI that is selected from:

(2S*,3S*,4S*,5R*)-4-carboxy-3-[N-(5-isopr pyl-2-methoxybenzyl)amino]-5-methyl-2-phenylpyrrolidine and

(2S*,3S*,5S*)-5-carboxy-3-[N-(2-methoxy-5-trifluoromethoxybenzyl)amino]-2-phenylpiperidine.

The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkenyl", as used herein, unless otherwise indicated, refers to straight or branched hydrocarbon chain radicals having one double bond including, but not limited to, ethenyl, 1- and 2-propenyl, 2-methyl-1-propenyl, 1- and 2-butenyl.

The term "alkoxy", as used herein, unless otherwise indicated, refers to -O-alkyl, wherein alkyl is defined as above, and includes, but is not limited to methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy and t-butoxy.

The term "alkylthio", as used herein, unless otherwise indicated, refers to -S-alkyl, wherein alkyl is defined as above, and includes, but is not limited to methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, and t-butylthio.

The term "cycloalkyl", as used herein, unless otherwise indicated, refers to cyclic hydrocarbon radicals including, but not limited to cyclopropyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "one or more substituents," as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "excess lacrimation", as used herein, refers to a degree of lacrimation that is higher than the desired degree of lacrimation.

Compounds of the formulae I, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX and XXI contain chiral centers and ther fore exist in different enantiomeric forms. Th above definitions f these compounds include all optical isomers and all st reoisomers of such compounds, and mixtures ther of.

Detailed Description of the Invention

The compounds of the formulae Ia, Ib, Ic, Id, Ie, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX and XXI may be prepared as described below. Unless otherwise indicated, in the discussion that follows, structural formulae Ia, Ib, Ic, Id, Ie, X, XI XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX and XXI and groups II, III, IV, V, VI, VII, VIII and IX are defined as above.

Compounds of the formula Ia and Ib may be prepared as described in United States Patent Application 988,653, which was filed on December 10, 1992. This application is incorporated herein by reference in its entirety.

Compounds of the formula Ic may be prepared as described in United States Patent Application 932,392, which was filed on August 19, 1992, and PCT Patent Application PCT/US 93/09407, which designates the United States and which was filed in the United States Receiving Office on October 7, 1993 and published as WO 94/13663 on June 23, 1994. These applications are incorporated herein by reference in their entirety.

Compounds of the formula Id may be prepared as described in PCT Patent Application PCT/US 92/03571, which designates the United States and which was filed in the United States Receiving Office on May 5, 1992 and published as WO 93/00331 on January 7, 1993. This application is incorporated herein by reference in its entirety.

Compounds of the formula Ie may be prepared as described in United States Patent Application 123,306, which was filed on September 17, 1993 and in PCT Patent Application PCT/IB 94/00221, which designates the United States and which was filed in the International Bureau on July 18, 1994. This application is incorporated herein by reference in its entirety.

When R^3 is a group of the formula II, the starting materials of the formula NH_2R^3 that are used in the preparation of compounds of the formulae Ia, Ib, Ic, Id and

Ie may be prepared as described in United States Patent 5,162,339, which issued on November 11, 1992. This patent is incorporated herein by reference in its entirety.

When R^3 is a group of the formula III, the starting materials of the formula NH_2R^3 that are used in the preparation of compounds of the formulae Ia, Ib, Ic, Id and Ie may be prepared as described in PCT Patent Application PCT/US 91/02853, which designates the United States, was filed in the United States Receiving Office on April 25, 1991 and was published as WO 91/18899 on December 12, 1991. This application is incorporated herein by reference in its entirety.

When R^3 is a group of the formula IV, V or VI, the starting materials of the formula NH_2R^3 that are used in the preparation of compounds of the formulae Ia, Ib, Ic, Id and Ie may be prepared as described in PCT Patent Application PCT/US 91/03369, which designates the United States, was filed on in the United States Receiving Office May 14, 1991 and was published as WO 92/01688 on February 6, 1992. This application is incorporated herein by reference in its entirety.

When R^3 is a group of the formula VII, the starting materials of the formula NH_2R^3 that are used in the preparation of compounds of the formulae Ia, Ib, Ic, Id and Ie may be prepared as described in United States Patent 5,232,929, which issued on August 3, 1993, United States Patent Application 800,667, filed November 27, 1991, PCT Patent Application PCT/US 91/02541, which designates the United States, was filed in the United States Receiving Office on April 12, 1991 and was published as WO 91/18878 on December 12, 1991, and PCT Patent Application PCT/US 92/00065, which designates the United States, was filed in the United States Receiving Office on January 14, 1992 and was publish d as WO 92/17449 on October 15, 1992. These applications ar incorporated herein by reference in their entir ty.

When R^3 is a group of the formula VIII, the starting materials of the formula NH_2R^3 that are used in the preparation of compounds of the formulae Ia, Ib, Ic, Id and Ie may be prepared as described in PCT Patent Application PCT/US 91/05776, which designates the United States, was filed in the United States Receiving Office on August 20, 1991 and was published as WO 92/06079 on April 16, 1992, United States Patent Application 800,667, filed November 27, 1991 and PCT Patent Application PCT/US 92/00065, which designates the United States, was filed in the United States Receiving Office on January 14, 1992 and was published as WO 92/17449 on October 15, 1992. These applications are incorporated herein by reference in their entirety.

When R^3 is a group of the formula IX, the starting materials of the formula NH_2R^3 that are used in the preparation of compounds of the formulae Ia, Ib, Ic, Id and Ie may be prepared as described in United States Patent Application Serial No. 719,884, filed June 21, 1991 and PCT Patent Application PCT/US 92/04697, which designates the United States and which was filed in the United States Receiving Office on June 11, 1992 and published as WO 93/00330 on January 7, 1993. These applications are incorporated herein by reference in their entirety.

Compounds of the formula X may be prepared as described in PCT Patent Application PCT/US 92/04002, which designates the United States, was filed in the United States Receiving Office on May 19, 1992 and was published as WO 92/15585 on September 17, 1992. This application is incorporated herein by reference in its entirety.

Compounds of the formula XI may be prepared as described in PCT Patent Application PCT/US 92/04697, which designates the United States, and which was filed in the United States Receiving Office on June 11, 1992 and published as WO 93/00330 on January 7, 1993. This application is incorporated herein by reference in its entirety.

Compounds of the formula XII may be prepared as described in PCT Patent Application PCT/US 92/07730, which designates the United States and which was filed in the United States Receiving Office on September 18, 1992 and published as WO 93/10073 on May 27, 1993. This application is incorporated herein by reference in its entirety.

Compounds of the formula XIII may be prepared as described in PCT Patent Application PCT/US 92/06819, which designates the United States and which was filed in the United States Receiving Office on August 20, 1992 and published as WO 93/06099 on April 1, 1993. This application is incorporated herein by reference in its entirety.

Compounds of the formula XIV may be prepared as described in United States Patent Application 885,110, which was filed on May 18, 1992 and in PCT Patent Application PCT/US 93/01429, which designates the United States and which was filed in the United States Receiving Office on February 23, 1993 and published as WO 93/23380 on November 25, 1993. These applications are incorporated herein by reference in their entirety.

Compounds of the formula XV may be prepared by the procedure described in PCT Patent Application PCT/US 92/04002, which designates the United States, was filed on May 19, 1992 and published as WO 92/20676 on November 26, 1992. This application is incorporated herein by reference in its entirety.

Compounds of the formula XVI may be prepared as described in United States Patent Application 026,382, which was filed on April 7, 1993, and PCT Patent Application PCT/US 93/11793, which designates the United States, and which was filed on December 10, 1993 in the U.S. Receiving Office and published as WO 94/20500 on September 15, 1994. These applications ar incorporated herein by reference in their entirety.

Compounds of th f rmula XVII may be prepared as described in PCT Patent Application PCT/US 93/09169, which

designates the United States and which was filed in the U.S. Receiving Office on September 30, 1993 and published as WO 94/10170 on May 11, 1994. This application is incorporated herein by reference in its entirety.

Compounds of the formula XVIII may be prepared as described in PCT Patent Application PCT/US 93/09168, which designates the United States and which was filed in the U.S. Receiving Office on September 30, 1993 and published as WO 94/08997 on April 28, 1994. This application is incorporated herein by reference in its entirety.

Compounds of the formula XIX may be prepared as described in PCT Patent Application PCT/JP 94/00781, which designates the United States and which was filed in the Japanese Receiving Office on May 13, 1994. This application is incorporated herein by reference in its entirety.

Compounds of the formula XX may be prepared as described in PCT Patent Application PCT/JP 94/01092, which designates the United States and was filed in the Japanese Receiving Office on July 5, 1994. This application is incorporated herein by reference in its entirety.

Compounds of the formula XXI may be prepared as described in PCT Patent Application PCT/JP 94/01514, which designates the United States and was filed in the Japanese Receiving Office on September 13, 1994. This application is incorporated herein by reference in its entirety.

The compounds of the formulae Ia, Ib, Ic, Id, Ie, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII and XIX (hereinafter referred to, collectively, as the "therapeutic agents") and the pharmaceutically acceptable salts thereof are useful as substance P receptor antagonists, i.e., they possess the ability to antagonize the effects of tachykinins at the substance P receptor site in mammals. They and other NK-1 antagonists are able to function as therapeutic agents in the treatment and prevention of disorders of the eye such as glaucoma, ocular hypertension, miosis, excess lacrimation,

and breakdown of the blood aqueous barrier in mammals, including humans.

The therapeutic agents that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Examples of acids that form suitable pharmaceutically acceptable salts for use in this invention are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a therapeutic agent from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base therapeutic agents of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

Those therapeutic agents of this invention that are also acidic in nature are capabl of forming base salts with various pharmacologically acceptabl cations. The chemical bases that are used as reagents to prepare the pharmaceutically acceptable base salts of the therapeutic

ag nts are th se that form non-toxic base salts with the acidic therapeutic agents. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of th acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

As indicated above, therapeutic agents and their pharmaceutically acceptable salts exhibit substance P receptor binding activity. They and other NK-1 antagonists are of value in the treatment and prevention of glaucoma, ocular hypertension, miosis, excess lacrimation and breakdown of the blood aqueous barrier in mammals, including humans.

Other substance P receptor antagonists that are expected to exhibit activity for the treatment and prevention of the foregoing eye disorders in mammals, including humans, are those compounds described in the following references: European Patent Application EP 499,313, published August 19, 1992; European Patent Application EP 520,555, published December 30, 1992; European Patent Application EP 522,808, published January 13, 1993, European Patent Application EP 528,495, published February 24, 1993, PCT Patent Application WO 93/14084, published July 22, 1993, PCT Patent Application WO 93/01169, published January 21, 1993, PCT Patent Application WO 93/01165, published January 21, 1993, PCT Patent Application

WO 93/01159, published January 21, 1993, PCT Patent Application WO 92/20661, published November 26, 1992, European Patent Application EP 517,589, published December 12, 1992, European Patent Application EP 428,434, published May 22, 1991, and European Patent Application EP 360,390, published March 28, 1990.

The therapeutic agents and the pharmaceutically acceptable salts thereof, as well as other NK-1 antagonists, can be administered via either the oral, topical or parenteral routes. In general, these compounds are most desirably administered in dosages ranging from about 5.0 mg up to about 1500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.001 mg to about 21 mg per kg of body weight per day is most desirably employed. The preferred dosage for oral administration is from about 0.001 to about 5 mg per kg of body weight per day. Ointments or eyedrops will preferably contain the active agent in a concentration of about 0.01 to about 5 percent, more preferably about 1%.

Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The therapeutic agents, and their pharmaceutically acceptable salts, as well as other NK-1 antagonists may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the routes

previously indicat d, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, suppositories, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutic compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic agent in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The activity of the therapeutic agents as substance P receptor antagonists may be determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonizing activity of the herein described compounds may be evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic IC_{50} values for each compound tested.

In this procedure, bovine caudate tissue is removed from a -70°C freezer and homogenized in 50 volumes (w./v.) of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty-minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM f

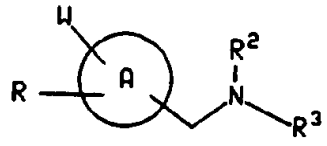
calcium chloride, 2 mM of magnesium chloride, 4 μg/ml of bacitracin, 4μg/ml of leupeptin, 2μg of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100 μl of the test compound made up to a concentration of 1 μM, followed by the addition of 100 μl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 μl of the tissue preparation produced as described above. The final volume is thus 1.0 ml, and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC_{50} values are calculated by using standard statistical methods.

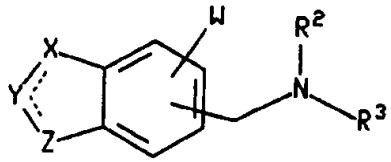
CLAIMS

1. A method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, comprising administering to said mammal

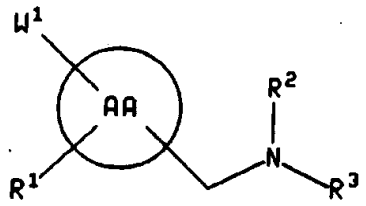
(a) an amount of a compound of the formula



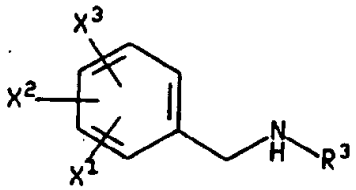
Ia



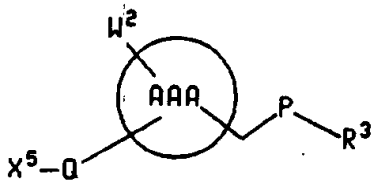
Ib



Ic



Id



Ie

wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the sidechain containing NR^2R^3 is attached t a carbon atom of ring system A;

AA is an aryl group selected from phenyl, naphthyl, thienyl, dihydroquinolinyl and indolinyl, and wherein the sidechain containing NR^2R^3 is attached to a carbon atom of AA;

AAA is an aryl group selected from phenyl, naphthyl, thienyl, dihydroquinolinyl and indolinyl, and wherein the $-CH_2PR^3$ sidechain is attached to a carbon atom of ring AAA;

P is NR^2, O, S, SO or SO_2;

Q is SO_2, NH, $-\overset{|}{N}(C_1-C_6)$alkyl or (C_1-C_6)alkyl$-\overset{|}{N}-SO_2-$

wherein the point of attachment of said (C_1-C_6)alkyl$-\overset{|}{N}-SO_2-$ to ring AAA is the nitrogen atom and the point of attachment to X^3 is the sulfur atom;

W^1 is hydrogen, halo or (C_1-C_6) alkyl, S-(C_1-C_3)alkyl, halo or (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms;

W^2 is hydrogen, (C_1-C_6)alkyl, S-(C_1-C_3)alkyl, halo or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

W is hydrogen, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, $-S(O)_v-(C_1-C_6)$ alkyl wherein v is zero, one or two, halo or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydr xy, phenyl, cyano, amino, (C_1-C_6)-

alkylamino, di-(C_1-C_6)alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)-

alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NHCH(=O) and -NHC(=O)-(C_1-C_6) alkyl;

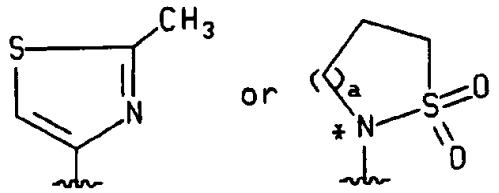
X^5 is a four to six membered heterocyclic ring containing from one to three heteroatoms selected from sulfur, nitrogen and oxygen (e.g., thiazolyl, pyrrolyl, thienyl, triazolyl, oxazolyl, oxadiazolyl, thiadiazolyl or imidazolyl), wherein said heterocyclic ring may optionally be substituted with from one to three substituents, preferably with from zero to two substituents, independently selected from phenyl, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms and halo;

R is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, or oxazolyl) wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms;

R^1 is selected from amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, -S(O)$_v$-(C_1-C_{10})-alkyl wherein v is zero, one or two, -S(O)$_v$-aryl wherein v is zero, one or two, -O-aryl, -$SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6

carbons, $-NHC(=O)(C_1-C_6)alkyl$, $-NHC(=O)CF_3$, $(C_1-C_{10})alkyl-N(-)-SO_2-(C_1-C_{10})alkyl$ wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and $(C_1-C_{10})alkyl-N(-)-SO_2-aryl$; and wherein the aryl moieties of said $-S(O)_v-aryl$, $-O-aryl$ and $(C_1-C_{10})alkyl-N(-)-SO_2-aryl$ are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$ and halo;

or R^1 is a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the $R^2R^3NCH_2$ side chain;

the dotted lines in formula Ib represent that one of the X-Y and Y-Z bonds may optionally be a double bond;

X is selected from =CH-, $-CH_2-$, -O-, -S-, -SO-, $-SO_2-$, $-N(R^4)-$, -NH-, =N-, $-CH[(C_1-C_6)alkyl]-$, $=C[(C_1-C_6)alkyl]-$, $-CH(C_6H_5)-$ and $=C(C_6H_5)-$;

Y is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2-$, $=C[(C_1-C_6)alkyl]-$, $-CH[(C_1-C_6)alkyl]-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, =N-, -NH-, $-N(R^4)-$, =C(halo)-, $=C(OR^4)-$, $=C(SR^4)-$, $=C(NR^4)-$, -O-, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)-$ and $-CH(C_6H_5)-$ may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of said $=[(C_1-C_6)alkyl]-$ and $-CH[C_1-C_6)alkyl]-$ may optionally be substituted with from on to three fluorine atoms;

Z is selected from =CH-, $-CH_2-$, =N-, -NH-, -S-,

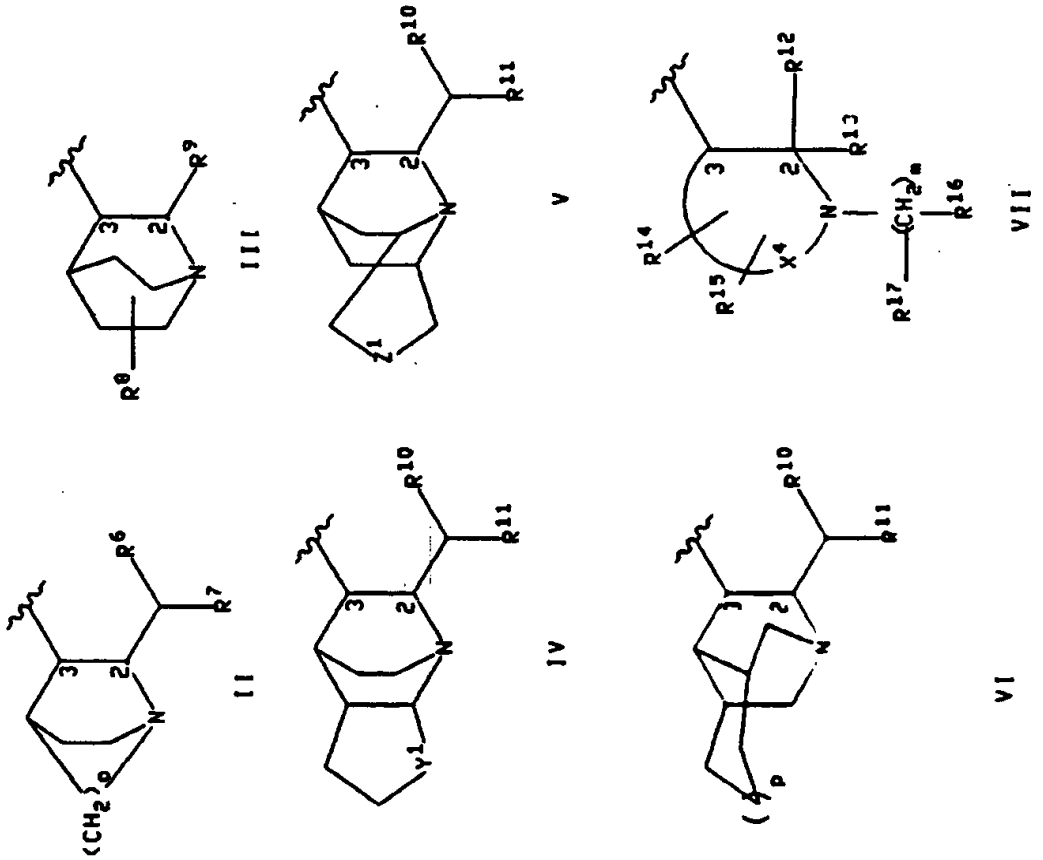
$-N(R^4)-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, $=C[(C_1-C_6)$ alkyl$]-$ and $-CH[(C_1-C_6)$alkyl$]-$;

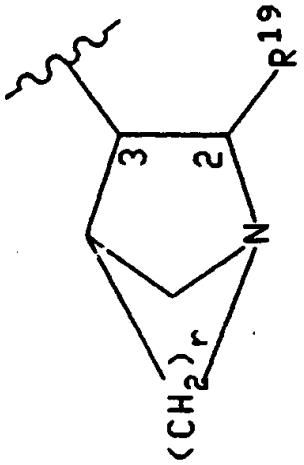
or X, Y and Z, together with the two carbon atoms shared between the benzo ring and the XYZ ring, form a fused pyridine or pyrimidine ring;

R^4 is (C_1-C_6) alkyl or phenyl;

R^2 is hydrogen or $-CO_2(C_1-C_{10})$alkyl;

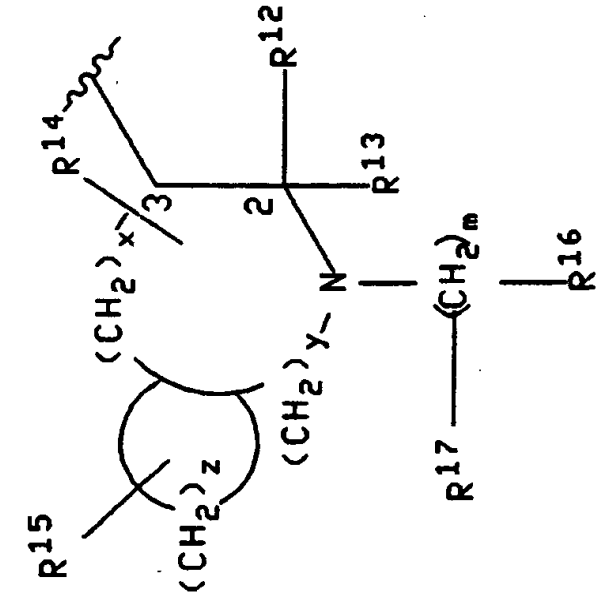
R^3 is selected from


II
III
IV
V
VI
VII



IX

and



VIII

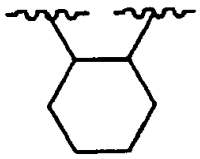
wherein R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl, wherein said phenyl may optionally be substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

R^7 is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^6;

R^8 is hydrogen or (C_1-C_6) alkyl;

R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y^1 is $(CH_2)_l$ wherein l is an integer from one to three, or Y^1 is a group of the formula



(J)

;

Z^1 is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

x is an integer from zero to four;

y is an integer from zero to four;

z is an integer from one to six, wherein the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbons of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

o is two or three;

p is zero or one;

r is ne, two or three;

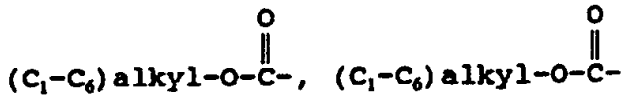
R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

X^4 is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};

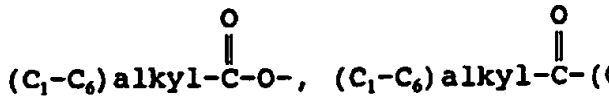
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};

R^{12} is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7)cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10})alkyl optionally substituted with from ne to three fluorine atoms, (C_1-C_{10})alkoxy ptionally substituted with

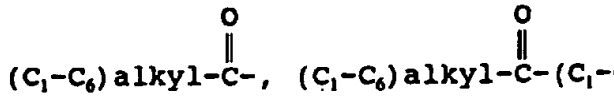
from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino,



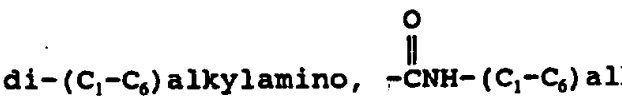
(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl,



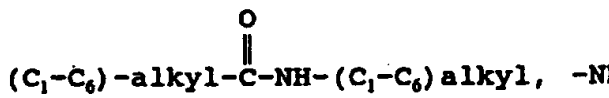
(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,



(C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-,



di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl,

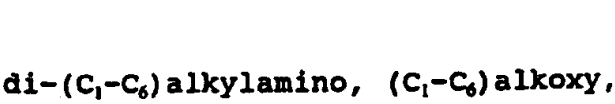


(C_1-C_6)-alkyl-C-NH-(C_1-C_6)alkyl, -NHCH and -NHC-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

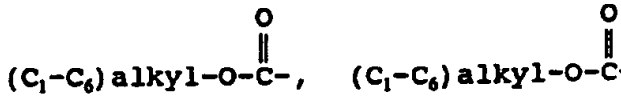
R^{13} is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to it may optionally be replaced by oxygen, nitrogen or sulfur;

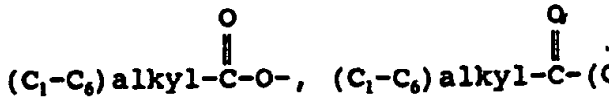
R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino,



di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C-OH,



(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl,



(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,

(C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^{12};

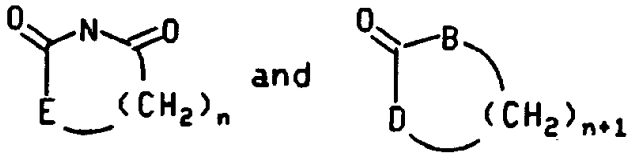
R^{16} is $NHCR^{18}$(=O), $NHCH_2R^{18}$, SO_2R^{18}, GR^{20} CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};

R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and

R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

G is selected from the group consisting of CH_2, nitrogen, oxygen, sulfur and carbonyl;

R^{20} is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



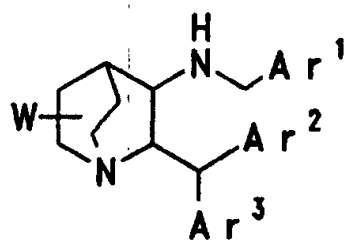
wherein B and D are selected from carbon, oxygen, and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; and any one of the carbons of the $(CH_2)_n$ or $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl, and either any two of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbons of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon

atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula VIII, R^{14} and R^{15} cannot be attached to the same carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, (C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} cannot both be hydrogen; (e) when R^{14} or R^{15} is attached to a carbon atom of X^4 or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom; and (f) neither R^{14}, R^{15}, R^{16} nor R^{17} can form a ring with R^{13};

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder; or

(b) an amount of a compound having the formula



(X)

wherein W is Y or $X(CH_2)_n$;

Y is optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl or optionally substituted (C_3-C_8)cycloalkyl;

X is optionally substituted (C_1-C_6)alkoxy, hydroxy, $CONR^1R^2$, CO_2R^1, CHR^1OR^2, $CHR^1NR^2R^3$, COR^1, $CONR^1OR^2$ r optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quin lyl, thienyl, furyl, oh noxyphenyl,

oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl; and n is an integer from zero to six;

Ar^1, Ar^2 and Ar^3 are each, independently, optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl;

and R^1, R^2 and R^3 are independently selected from hydrogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl; and optionally substituted (C_1-C_5)heterocyclic groups, wherein said heterocyclic groups are selected from pyrrolidino, piperidino, morpholino, piperazinyl and thiamorpholino;

and wherein the substituents on the foregoing substituted alkyl, alkenyl, cycloalkyl and alkoxy groups are independently selected from halo, nitro, amino, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, trifluoromethyl and trifluoromethoxy;

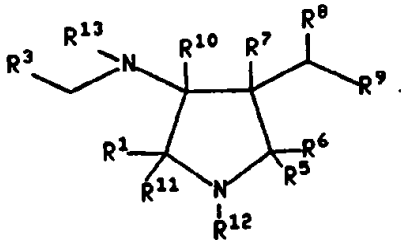
and wherein the substituents on the foregoing substituted (C_1-C_5) heterocyclic groups are attached to a sulfur or nitrogen atom on the ring and are independently selected from oxygen, di-oxygen and (C_1-C_4)alkyl when attached to a ring sulfur atom, and are independently selected from oxygen and (C_1-C_4)alkyl when attached to a ring nitrogen atom;

and wherein the substituents on said substituted Ar^1 groups are independently selected from (C_1-C_6)alkyl optionally substituted with from one to three halo groups, (C_1-C_6)alkox optionally substituted with from one to three halo group, (C_1-C_6)alkylsulfinyl, (C_2-C_6)alkenyl, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, and di-(C_1-C_6)alkylamino wherein one or both of the alkyl groups may be ptionally substituted with a (C_1-C_6)alkylsulfonyl, or (C_1-C_6)alkylsulfinyl group;

and wherein the substituents on said substituted Ar^2 and Ar^3 groups are independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl, di-(C_1-C_4)alkylamino, trifluoromethyl and trifluoromethoxy; with the proviso that when Y is unsubstituted or is substituted with (C_1-C_4)alkyl, it is attached to the 4- or 6-position of the quinuclidine ring;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder; or

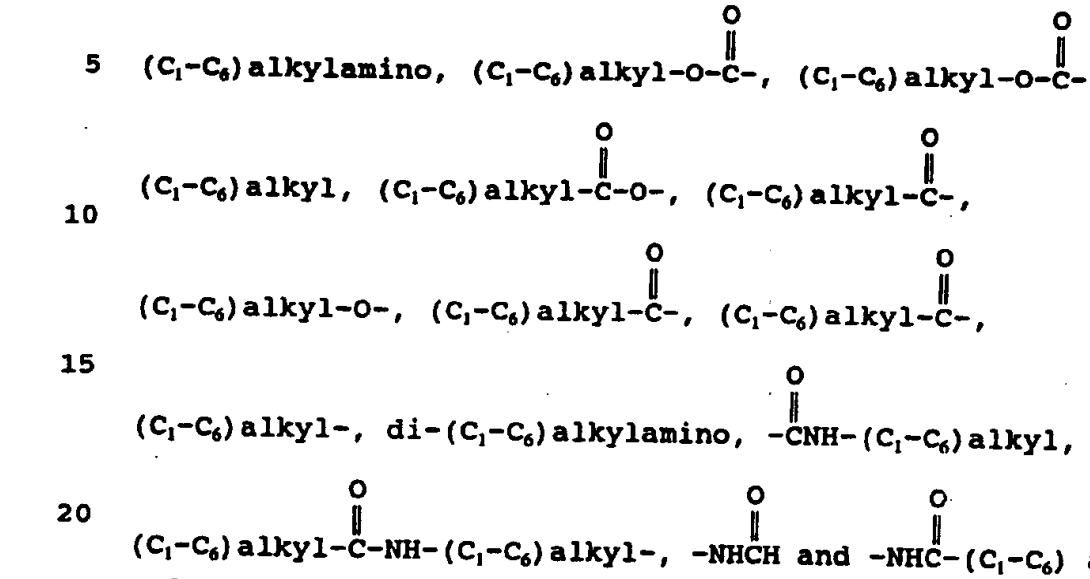
(c) A method of treating or preventing emesis in a mammal, comprising administering to said mammal an amount of a compound having the formula



(XI)

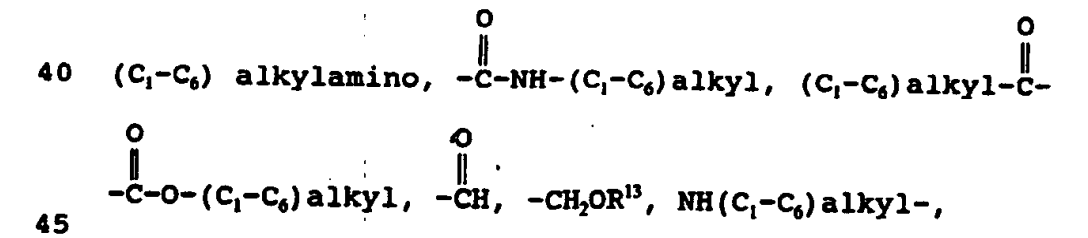
wherein R^1 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine

atoms, (C_1-C_6) alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy),



(C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-, -NHCH(=O) and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy substituted with from one to three fluorine atoms, amino, phenyl, trihaloalkoxy,



(C_1-C_6) alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-C(=O)-(C_1-C_6)alkyl, -CH(=O), $-CH_2OR^{13}$, NH(C_1-C_6)alkyl-,

$-NHCH$, $-NR^{24}C-(C_1-C_6)$alkyl and $-NHC-(C_1-C_6)$alkyl;

one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, (C_1-C_3)alkyl, (C_1-C_8)acyloxy-(C_1-C_3)alkyl, (C_1-C_8)alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl,

$HC-$, $R^{14}R^{15}NCO_2CH_2-$, $R^{16}OCO_2CH_2-$, (C_1-C_4)alkyl$-CO_2CH_2-$, $-CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2-$, $R^{19}OCO_2-$, $C_6H_5CH_2CO_2CH_2-$, $C_6H_5CO_2CH_2-$, (C_1-C_4)alkyl-$CH(OH)-$, $C_6H_5CH(OH)-$, $C_6H_5CH_2CH(OH)-$, CH_2halo, $R^{20}SO_2OCH_2$, $-CO_2R^{16}$ and $R^{21}CO_2-$;

R^{10} and R^{11} are independently selected from hydrogen, (C_1-C_3) alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula

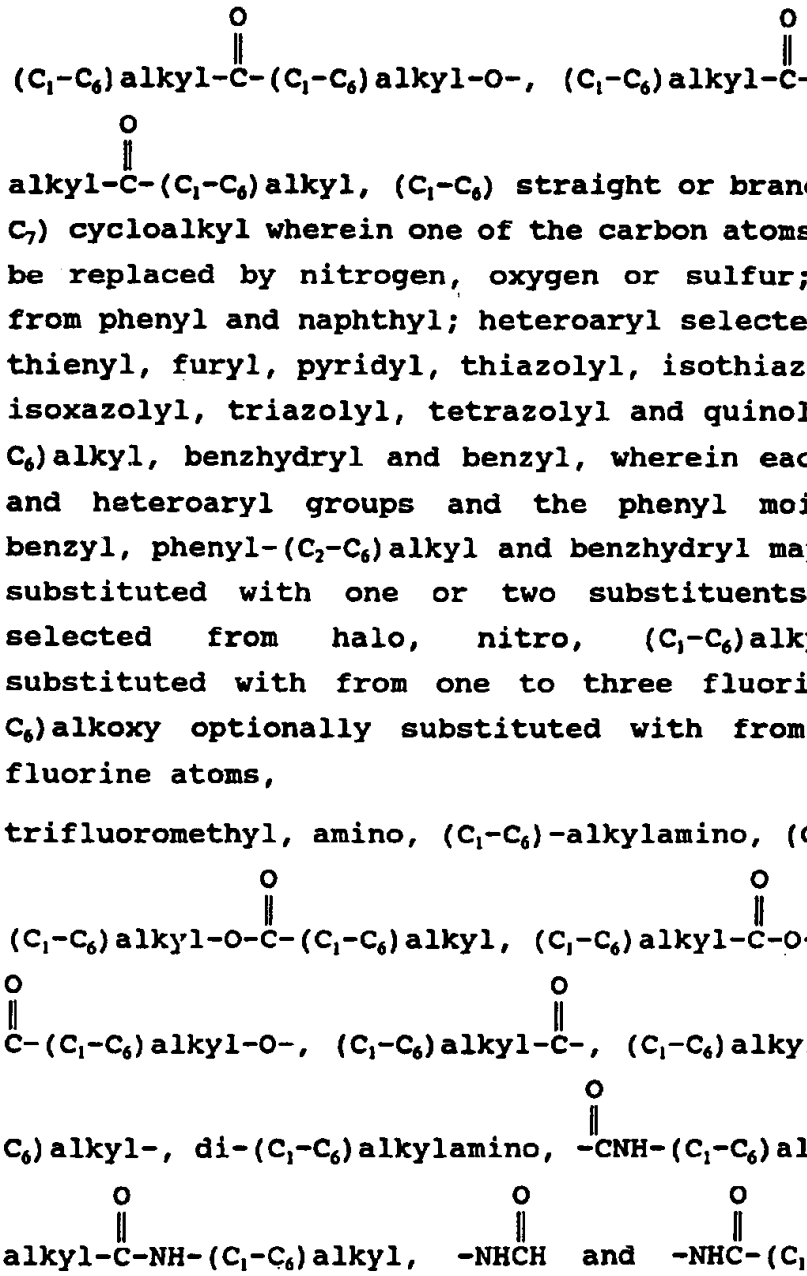
$$R^{22}-(CH_2)_m-\overset{R^{23}}{\underset{|}{}}$$

wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^{23};

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)-

alkyl$-O-C-$, (C_1-C_6)alkyl$-O-C-(C_1-C_6)$alkyl, (C_1-C_6)alkyl$-C-$,



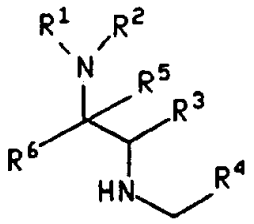
and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen f the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the provis that when R^9, together with the carbon to which it is attached, the

nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder; or

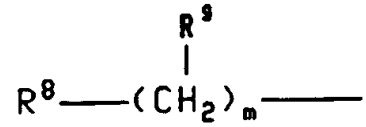
(d) an amount of a compound of the formula



XII

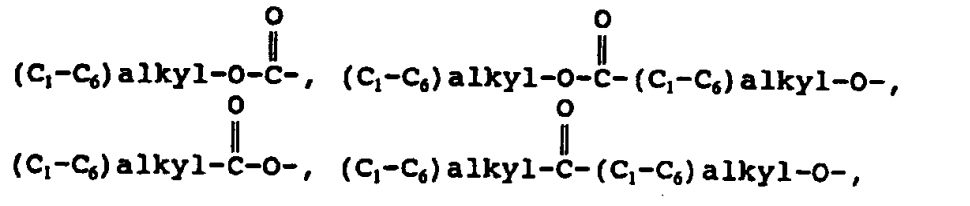
wherein R^1 is hydrogen, (C_1-C_8) alkyl, a saturated (C_6-C_{10}) carbocyclic ring system containing two fused rings, a saturated (C_6-C_{10}) carbocyclic bridged ring system containing two rings, or benzyl wherein the phenyl moiety of said benzyl may optionally be substituted with one or more substituents independently selected from halo, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_8) alkoxy optionally substituted with from one to three fluorine atoms;

R^2 is hydrogen, benzyl or a group of the formula



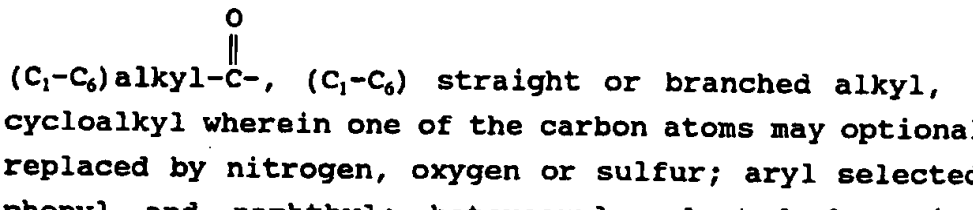
wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^9;

R^8 and R^9 are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy,

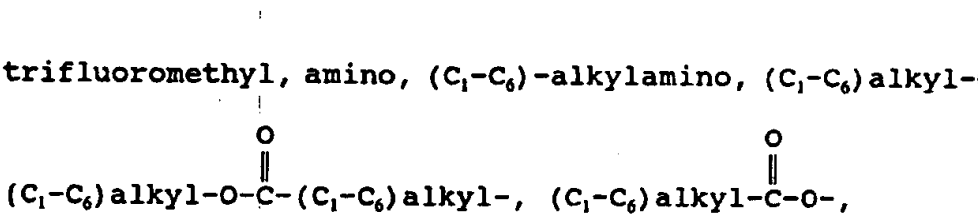


(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl-O-,

(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,



(C_1-C_6)alkyl-C-, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms,



trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C-,

(C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C-O-,

(C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C-,

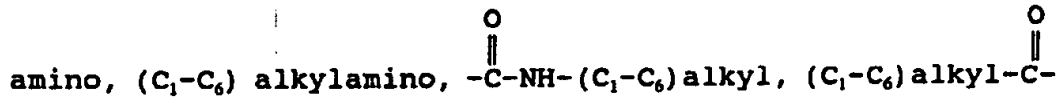
(C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino,

-CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C-NH-(C_1-C_6)alkyl, -NHCH and

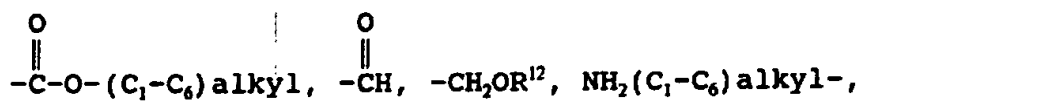
-NHC-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a saturated or unsaturated monocyclic ring containing from three to eight carbon atoms, a fused bicyclic ring containing from six to ten carbon atoms, or a saturated bridged ring system containing from six to ten carbon atoms;

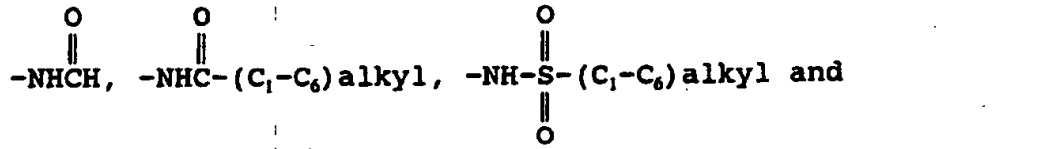
R^4 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having from three to seven carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one, two or three substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms, phenyl,



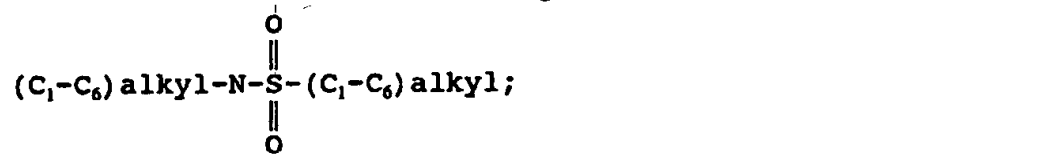
amino, (C_1-C_6) alkylamino, -C-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C-,



-C-O-(C_1-C_6)alkyl, -CH, $-CH_2OR^{12}$, $NH_2(C_1-C_6)$alkyl-,



-NHCH, -NHC-(C_1-C_6)alkyl, -NH-S-(C_1-C_6)alkyl and



(C_1-C_6)alkyl-N-S-(C_1-C_6)alkyl;

R^3 is hydrogen, (C_3-C_8)cycloalkyl, (C_1-C_6) straight or branched alkyl or phenyl optionally substituted with one or more substituents independently selected from halo, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, and (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

R^5 is hydrogen, (C_1-C_6)alkyl, or phenyl optionally substituted with one or more substituents independently selected from halo, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

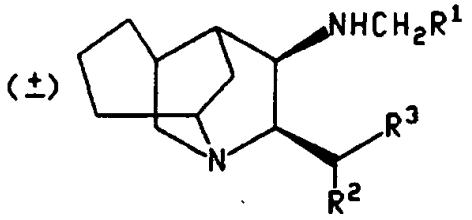
R^6 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, trifluoromethyl, amino, trihaloalkoxy (e.g.,trifluoromethoxy), (C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino,

$-\overset{O}{\overset{\|}{C}}NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)alkyl-$, $-NH\overset{O}{\overset{\|}{C}}H$ and $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)alkyl$; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl; and

R^{12} is hydrogen, $(C_1-C_3)alkyl$ or phenyl;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder;

(e) an amount of a compound of the formula



XIII

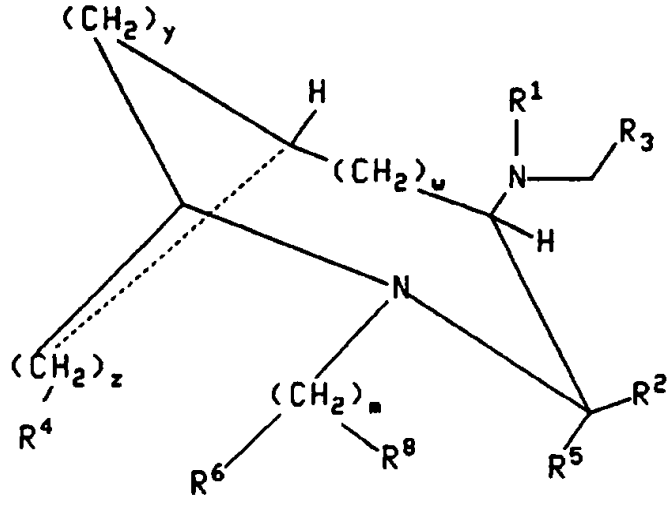
wherein R^1 is cycloalkyl having from five to seven carbon atoms, pyrrolyl, thienyl, pyridyl, phenyl or substituted phenyl, wherein said substituted phenyl is substituted with from one to three substituents independently selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety and benzyloxycarbonyl;

R^2 is furyl, thienyl, pyridyl, indolyl, biphenyl, phenyl or substituted phenyl, wherein said substituted phenyl is substituted with one or two substituents independently selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety and benzyloxycarbonyl; and

R^3 is thienyl, phenyl, fluorophenyl, chlorophenyl or br mophenyl;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder; or

(f) an amount of a compound of the formula



XIV

wherein m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

w is an integer from 0 to 2;

y is an integer from 1 to 4;

z is an integer from 1 to 4, and wherein any one of the carbon atoms of said $(CH_2)_z$ may optionally be substituted with R^4;

R^1 is hydrogen or (C_1-C_8) alkyl optionally substituted with hydroxy, alkoxy or fluoro;

R^2 is a group selected from hydrogen, (C_1-C_6)straight or branched alkyl, (C_3-C_7)cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, indanyl, and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl,

isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl(C_2-C_6)alkyl, benzhydryl and benzyl, wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)- (C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)- (C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)- (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl;

R^5 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^3 is aryl selected from phenyl, indanyl, and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three

fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, phenyl, amino, (C_1-C_6)alkylamino, (C_1-C_6)dialkyl amino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, $-\overset{O}{\overset{\|}{N}}HCH$ and $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl;

R^4 is independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl$-O-\overset{O}{\overset{\|}{C}}-$, (C_1-C_6)alkyl$-O-\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-O-$, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl$-O-$, hydroxy-$(C_1-C_6)$alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-$, (C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl-, and the groups set forth in the definition of R^2;

R^6 is $NH\overset{O}{\overset{\|}{C}}R^9$, $NHCH_2R^9$, $NHSO_2R^9$ or one of the groups set forth in any of the definitions of R^2, and R^4;

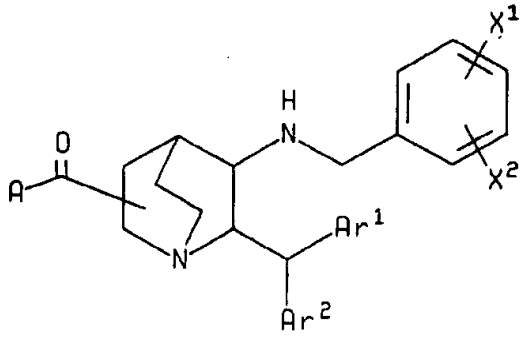
R^8 is oximino (=NOH) or one of the groups set forth in any of the definitions of R^2, and R^4;

R^9 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

with the proviso that (a) when m is 0, R^8 is absent and R^6 is hydrogen, (b) neither R^4, R^6, nor R^8 can form, together with the carbon to which it is attached, a ring with R^5, and (c) the sum of y and z must be less than 7;

or a pharmaceutically acceptable salt thereof, that is ffective in treating or preventing such disorder; or

(g) an amount of a compound of the formula



XV

wherein X^1 is (C_1-C_5) alkoxy or halosubstituted (C_1-C_5)alkoxy;

X^2 is hydrogen, halogen, (C_1-C_5)alkyl, (C_2-C_5)alkenyl, (C_2-C_5)alkynyl, (C_1-C_5)alkoxy, (C_1-C_5)alkylthio, (C_1-C_5)alkylsulfinyl, (C_1-C_5)alkylsulfonyl, halosubstituted (C_1-C_5)alkyl, halosubstituted (C_1-C_5)alkoxy, (C_1-C_5)alkylamino, dialkylamino having from 1 to 5 carbon atoms in each alkyl moiety, (C_1-C_5)alkylsulfonylamino (which may be substituted by halogen), (C_1-C_5)alkyl-N-(C_1-C_5)alkylsulfonyl (which may be substituted by halogen in the alkylsulfonyl moiety), (C_1-C_5)alkanoylamino (which may be substituted by halogen) or (C_1-C_5)alkyl-N-(C_1-C_5)alkanoyl (which may be substituted by halogen in the alkanoyl moiety);

Ar^1 and Ar_2 are each, independently, thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;

A is $Y-(CH_2)_m-CH(R^2)-(CH_2)_n-NR^1-$;

R^1 is hydrogen, (C_1-C_5)alkyl, benzyl or $-(CH_2)_p-Y$;

R^2 is hydrogen, (C_1-C_5)alkyl (which may be substituted by a substituent selected from the group consisting of hydroxy, amino, methylthio and mercapto), benzyl, 4-hydroxybenzyl, 3-indolylmethyl or $-(CH_2)_p-Y$;

Y is -CN, $-CH_2Z$ or -COZ;

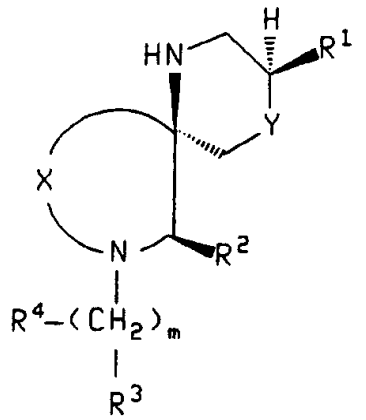
Z is hydroxy, amino, (C_1-C_5)alkoxy, (C_1-C_5)alkylamino or dialkylamino having from 1 to 5 carbon atoms in each alkyl moiety;

m, n and p are each, independently, 0, 1, 2 or 3; and

R^1 and R^2 may be connected to form a ring;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder; or

(h) an amount of a compound of the formula



XVI

wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino,

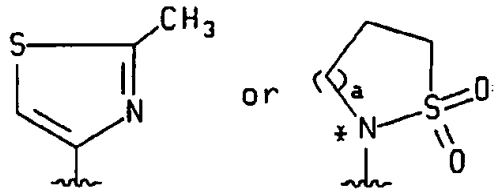
di-(C_1-C_6)alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl,

(C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-NH-($C_1$-$C_6$) alkyl, hydroxy($C_1$-$C_4$)alkyl,

$-\overset{O}{\overset{\|}{N}}HCH$, $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)$ alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-S(O)_v-(C_1-C_{10})$-alkyl wherein v is zero, on or two, $-S(O)_v$-aryl wherein v is zer , one or tw , -O-aryl, $-SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5,

together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, (C_1-C_{10})alkyl-N($|$)-SO_2-(C_1-C_{10})alkyl wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and (C_1-C_{10})alkyl-N($|$)-SO_2-aryl; and wherein the aryl moieties of said $-S(O)_v$-aryl, -O-aryl and (C_1-C_{10})alkyl-N($|$)-SO_2-aryl are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;

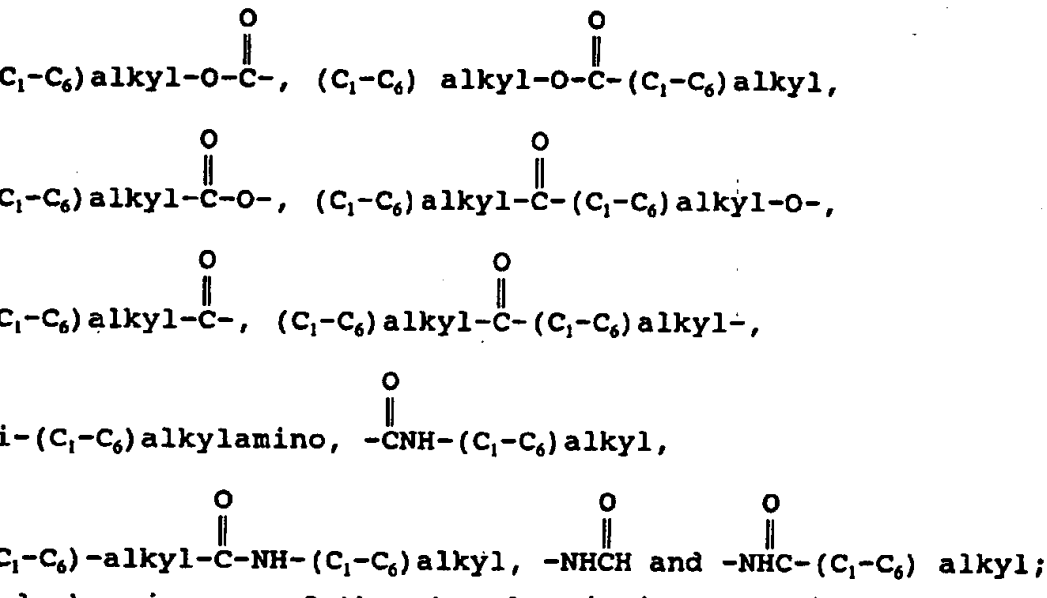
or R^1 is phenyl substituted with a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R^1;

R^2 is selected from (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three

fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino,



(C_1-C_6)alkyl-O-C-, (C_1-C_6) alkyl-O-C-(C_1-C_6)alkyl,

(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,

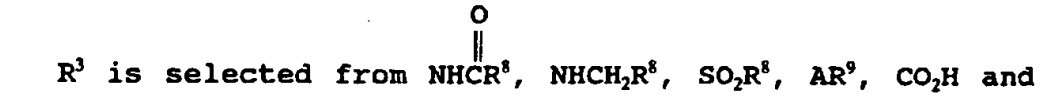
(C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-,

di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl,

(C_1-C_6)-alkyl-C-NH-(C_1-C_6)alkyl, -NHCH and -NHC-(C_1-C_6) alkyl;

and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;



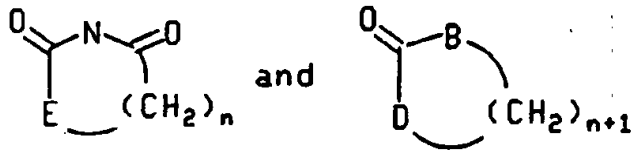
R^3 is selected from NHCR^8, NHCH_2R^8, SO_2R^8, AR^9, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;

A is CH_2, nitrogen, oxygen, sulfur or carbonyl;

R^8 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

R^4 is selected from oximino (=NOH) and the radicals set forth in the definitions of R^2, R^6 and R^7;

R^9 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;

R^6 and R^7 are independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, $-\overset{O}{\overset{\|}{C}}-OH$,

(C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,

(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-,

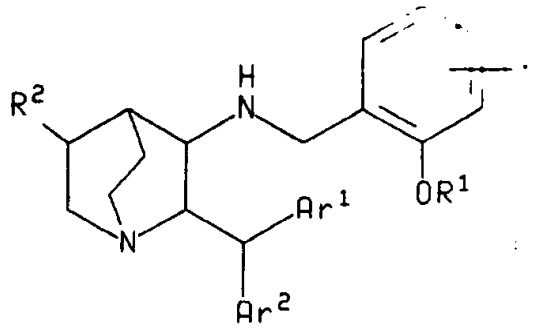
(C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl- and the radicals set forth in the definition of R^2; and

Y is $(CH_2)_z$ wherein z is zero or one;

with the proviso that: (a) when A is $-(CH_2)-$ or carbonyl, R^9 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; and (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder; or

(i) an amount of a compound of the formula



XVII

wherein Ar^1 and Ar^2 are each independently aryl or substituted aryl;

R^1 is alkyl having from 1 to 6 carbon atoms;

R^2 is hydrogen or alkyl having from 1 to 6 carbon atoms;

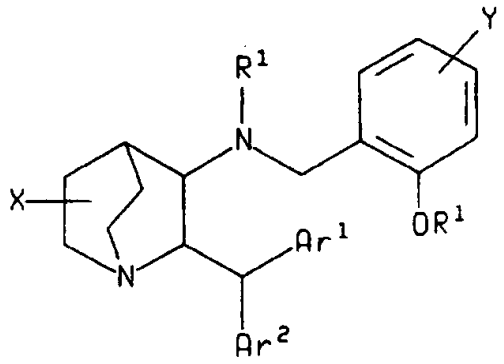
and either X and Y are taken separately and they are each, independently, hydrogen, dialkylphosphoryl having from 2 to 12 carbon atoms, alkyl having from 1 to 6 carbon atoms; or X and Y are taken together and they represent a hydrocarbon chain having 3, 4, or 5 carbon atoms, optionally containing up to 2 double bonds and optionally having 1 or 2 substituents selected from oxo, hydroxy and alkyl having from 1 to 6 carbon atoms;

provided that when X and Y are taken together they are attached to adjacent carbon atoms; and

provided that if either X or Y is hydrogen, then the other one must be alkenyl or alkynyl;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder; or

(j) an amount of a compound of the formula



XVIII

wherein Ar^1 and Ar^2 are each, independently, thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;

X is $-CONR^3R^4$, $-CO_2R^3$, CH_2OR^3, $-CH_2NR^3R^4$ or $-CONR^3OR^4$;

R^1, R^3 and R^4 are each, independently, hydrogen or alkyl having 1 to 4 carb n atoms;

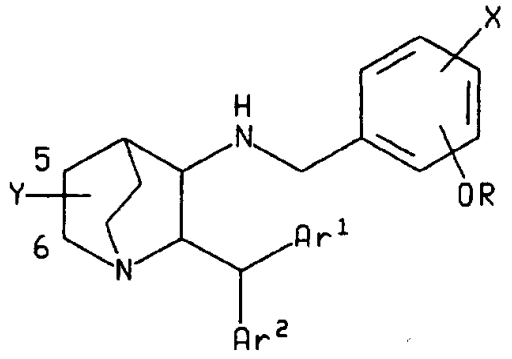
R^2 is alkyl having 1 to 4 carbon atoms;

Y is alkylsulfonyl having 1 to 4 carbon atoms, N-alkyl-N-alkanoylamino (which may be substituted by halogen in the

alkanoyl moiety) having 1 to 4 carbon atoms in the alkyl and the alkanoyl moieties, N-alkyl-N-alkylsulfonylamino (which may be substituted by halogen in the alkylsulfonyl moiety) having 1 to 4 carbon atoms in the alkyl and the alkyl sulfonyl moieties, alkenyl having 2 to 4 carbon atoms, alkynyl having 2 to 4 carbon atoms, halosubstituted alkyl having 1 to 4 carbon atoms, alkylamino having 1 to 4 carbon atoms, alkanoylamino (which may be substituted by halogen) having 1 to 4 carbon atoms or alkylsulfonylamino (which may be substituted by halogen) having 1 to 4 carbon atoms;

or a pharmaceutically acceptable salt thereof that is effective in treating or preventing disorder; or

(k) an amount of a compound of the formula



XIX

wherein R is C_1-C_6 alkyl;

X is C_1-C_6 alkyl having one or more substituents bonded through a heteroatom;

Ar^1 and Ar^2 are each, independently, aryl optionally substituted by one C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, cyano, nitro, phenoxy, mono C_1-C_6 alkylamino, di C_1-C_6 alkylamino, halosubstituted C_1-C_6 alkyl, or halosubstituted C_1-C_6 alk xy;

Y is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, $Z-(CH_2)_p-$, or $W-(CH_2)_m-CHR^2-(CH_2)_n-NR^1CO-$ wherein Y is at the 4-, 5- or 6-position on the quinuclidine ring;

R^1 is hydrogen, C_1-C_6 alkyl, benzyl or $-(CH_2)_r-W$;

R^2 is hydrogen or C_1-C_6 alkyl which may be substituted by one hydroxy, amino, methylthio, mercapto, benzyl, 4-hydroxybenzyl, 3-indolylmethyl or $-(CH_2)_r-W$;

Z is C_1-C_6 alkoxy, $-CONR^4R^5$, $-CO_2R^4$, $-CHR^4OR^5$, $-CHR^4NR^5R^6$, $-COR^4$, $-CONR^4OR^5$ or optionally substituted aryl;

each W is independently cyano, hydroxymethyl, C_2-C_6 alkoxymethyl, aminomethyl, mono C_1-C_6 alkylaminomethyl, di C_1-C_6 alkylaminomethyl, carboxyl, carbamoyl or C_1-C_6 alkoxycarbonyl;

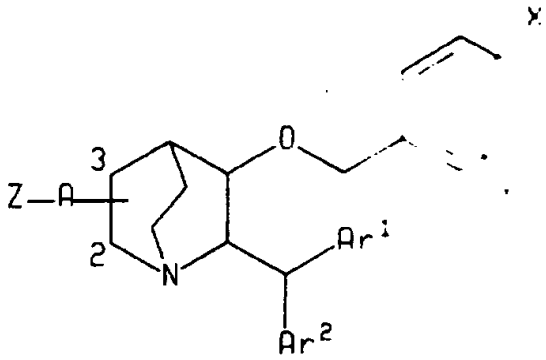
R^4, R^5 and R^6 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl or an optionally substituted aryl or heterocyclic group;

p is 0 to 6; and

m, n and r are each, independently, 0 to 3;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorders; or

(l) an amount of a compound of the formula



XX

wherein X and Y are each hydrogen, halo, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl or tri C_1-C_6 alkylsilyl;

Ar^1 and Ar^2 are each aryl optionally substituted by halo;

A is -CO- or $-(CH_2)-$;

Z-A- is at the 2 or 3 position on the quinuclidine ring;

Z is hydroxy, C_1-C_6 alkoxy, NR^1R^2 or W^1-$(CH_2)_m$-CHR^4-$(CH_2)_n$-NR^3 wherein

R^1 and R^2, when taken separately, are each hydrogen or C_1-C_6 alkyl;

R^1 and R^2, when taken together with the nitrogen atom to which they are attached, represent piperidino, pyrrolidino, morpholino, thiomorpholino or piperazino;

R^3 is hydrogen, C_1-C_6 alkyl, benzyl or -$(CH_2)_r$-W^2;

R^4 is hydrogen or C_1-C_6 alkyl which may be substituted by hydroxy, amino, methylthio, mercapto, benzyl, 4-hydroxylbenzyl, 3-indolylmethyl or -$(CH_2)_s$-W^3;

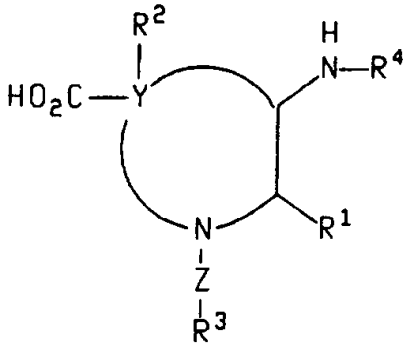
R^3 and R^4, when taken together, represent CH_2 or CH_2CH_2;

W^1, W^2 and W^3 are each cyano, hydroxymethyl, C_2-C_6 alkoxymethyl, aminomethyl, (C_1-C_6 alkylamino)methyl, (di C_1-C_6 alkylamino)methyl, carboxyl, (C_1-C_6 alkyl)carbamoyl, or (di C_1-C_6 alkyl)carbamoyl, carbamoyl or (C_1-C_6 alkoxy)carbonyl; and

m, n, r and s are each 0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof that is effective in treating or preventing such disorder; or

(m) an amount of a compound of the formula



XXI

wherein Y is C_2-C_4 alkylene;

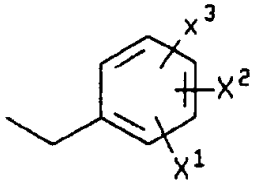
Z is a valence bond or C_1-C_6 alkylene;

R^1 is phenyl, biphenyl, indanyl, naphthyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, tetrazolyl, quinolyl, phenyl C_1-C_6 alkyl- or benzhydryl, wherein each of the ring moieties may optionally be substituted by one or more substituents independently selected from halogen, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkyl, C_1-C_6 alkoxy and halosubstituted C_1-C_6 alkoxy;

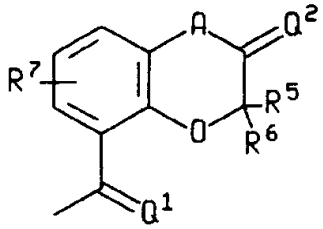
R^2 is hydrogen or C_1-C_6 alkyl;

R^3 is hydrogen, hydroxy, cyano, amino or carboxy; and

R^4 represents a group of the formula (II) or (III)



II



III

wherein X^1, X^2 and X^3 are each halo, hydrogen, nitro, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkoxy, halosubstituted C_1-C_6 alkoxy, hydroxy, amino, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl or C_1-C_6 alkylsulfonyl;

Q^1 and Q^2 are each H_2, oxygen or sulfur;

A is valence bond, methylene, oxygen, sulfur or NH;

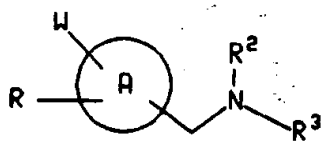
R^5 and R^6 are each hydrogen or C_1-C_6 alkyl; and

R^6 is hydrogen, halogen, C_1-C_6 alkyl, halosubstituted C_1-C_6 alkyl or C_1-C_6 alkoxy;

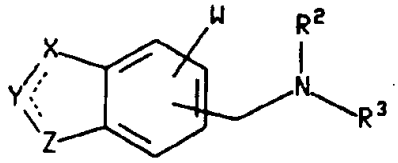
provided that when Z is a valence bond, R^3 must be hydrogen;

or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

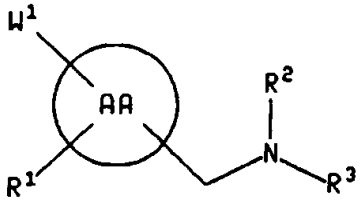
2. A method according to claim 1, wherein the compound administered is a compound of the formula



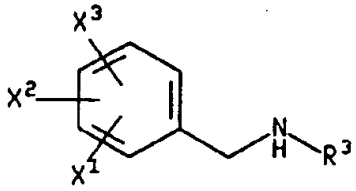
Ia



Ib



Ic



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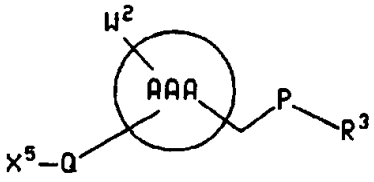


Ie

wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the sidechain containing NR^2R^3 is attached to a carbon atom of ring system A;

AA is an aryl group selected from phenyl, naphthyl, thienyl, dihydroquinolinyl and indolinyl, and wherein the sidechain containing NR^2R^3 is attached to a carbon atom of AA;

AAA is an aryl group selected from phenyl, naphthyl, thienyl, dihydroquinolinyl and indolinyl, and wherein the $-CH_2PR^3$ sidechain is attached to a carbon atom of ring AAA;

P is NR^2, O, S, SO or SO_2;

Q is SO_2, NH, $-\overset{|}{N}(C_1-C_6)$alkyl or (C_1-C_6)alkyl$-\overset{|}{N}-SO_2-$

wherein the point of attachment of said (C_1-C_6)alkyl$-\overset{|}{N}-SO_2-$ to ring AAA is the nitrogen atom and the point of attachment to X^5 is the sulfur atom;

W^1 is hydrogen, halo or (C_1-C_6) alkyl, S-(C_1-C_3)alkyl, halo or (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms;

W^2 is hydrogen, (C_1-C_6)alkyl, S-(C_1-C_3)alkyl, halo or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

W is hydrogen, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, $-S(O)_v-(C_1-C_6)$ alkyl wherein v is zero, one or two, halo or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-

alkylamino, di-(C_1-C_6)alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)

alkyl-$\overset{O}{\overset{\|}{C}}$-NH-($C_1$-$C_6$) alkyl, hydroxy($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy($C_1$-$C_4$)alkyl, -NHC$\overset{O}{\overset{\|}{H}}$ and -NH$\overset{O}{\overset{\|}{C}}$-($C_1$-$C_6$) alkyl;

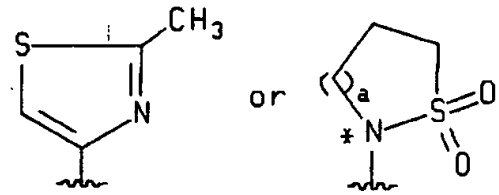
X^5 is a four to six membered heterocyclic ring containing from one to three heteroatoms selected from sulfur, nitrogen and oxygen (e.g., thiazolyl, pyrrolyl, thienyl, triazolyl, oxazolyl, oxadiazolyl, thiadiazolyl or imidazolyl), wherein said heterocyclic ring may optionally be substituted with from one to three substituents, preferably with from zero to two substituents, independently selected from phenyl, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms and halo;

R is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, or oxazolyl) wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms;

R^1 is selected from amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, -S(O)$_v$-(C_1-C_{10})-alkyl wherein v is zero, one or two, -S(O)$_v$-aryl wherein v is zero, one or two, -O-aryl, -$SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6

carbons, $-NHC(=O)(C_1-C_6)alkyl$, $-NHC(=O)CF_3$, $(C_1-C_{10})alkyl-N(-)-SO_2-(C_1-C_{10})alkyl$ wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and $(C_1-C_{10})alkyl-N(-)-SO_2-aryl$; and wherein the aryl moieties of said $-S(O)_v-aryl$, $-O-aryl$ and $(C_1-C_{10})alkyl-N(-)-SO_2-aryl$ are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$ and halo;

or R^1 is a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the $R^2R^3NCH_2$ side chain;

the dotted lines in formula Ib represent that one of the X-Y and Y-Z bonds may optionally be a double bond;

X is selected from =CH-, $-CH_2-$, -O-, -S-, -SO-, $-SO_2-$, $-N(R^4)-$, -NH-, =N-, $-CH[(C_1-C_6)alkyl]-$, $=C[(C_1-C_6)alkyl]-$, $-CH(C_6H_5)-$ and $=C(C_6H_5)-$;

Y is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2-$, $=C[(C_1-C_6)alkyl]-$, $-CH[(C_1-C_6)alkyl]-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, =N-, -NH-, $-N(R^4)-$, =C(halo)-, $=C(OR^4)-$, $=C(SR^4)-$, $=C(NR^4)-$, -O-, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)-$ and $-CH(C_6H_5)-$ may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of said $=[(C_1-C_6)alkyl]-$ and $-CH[C_1-C_6)alkyl]-$ may optionally be substituted with from one to three fluorine atoms;

Z is selected from =CH-, $-CH_2-$, =N-, -NH-, -S-,

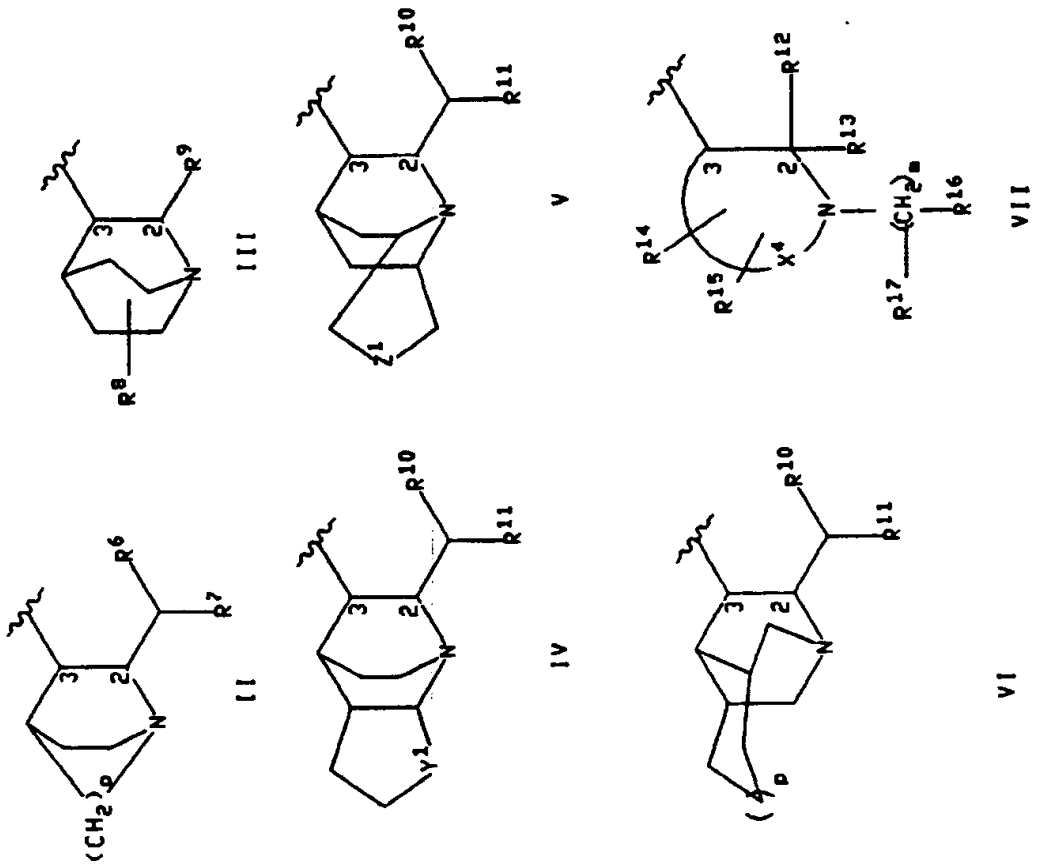
$-N(R^4)-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, $=C[(C_1-C_6)$ alkyl$]-$ and $-CH[(C_1-C_6)$alkyl$]-$;

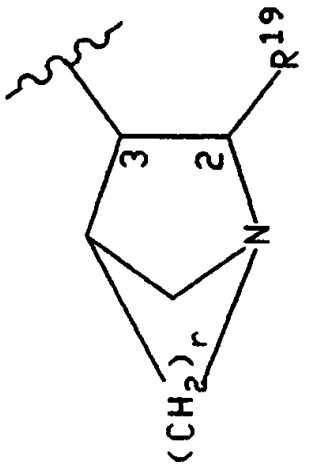
or X, Y and Z, together with the two carbon atoms shared between the benzo ring and the XYZ ring, form a fused pyridine or pyrimidine ring;

R^4 is (C_1-C_6) alkyl or phenyl;

R^2 is hydrogen or $-CO_2(C_1-C_{10})$alkyl;

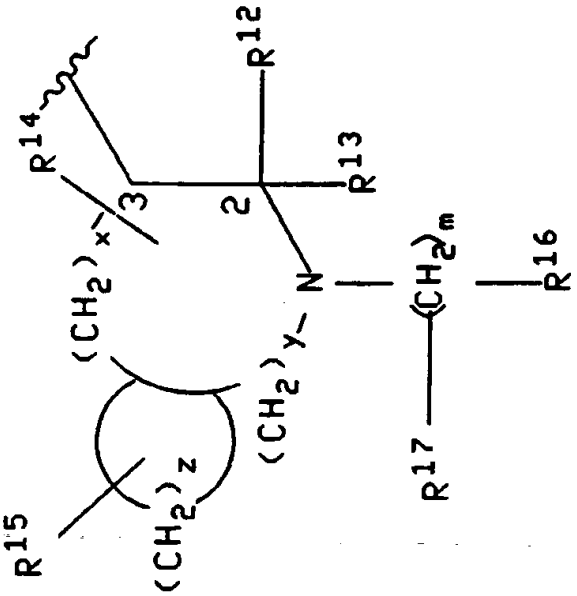
R^3 is selected from


II
III
IV
V
VI
VII



IX

and



VIII

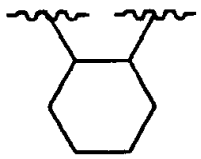
wherein R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl, wherein said phenyl may optionally be substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

R^7 is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^6;

R^8 is hydrogen or (C_1-C_6) alkyl;

R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y^1 is $(CH_2)_l$ wherein l is an integer from one to three, or Y^1 is a group of the formula



(J)

;

Z^1 is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;

x is an integer from zero to four;

y is an integer from zero to four;

z is an integer from one to six, wherein the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbons of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;

o is two or three;

p is zero or one;

r is one, two or three;

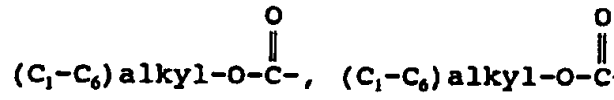
R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

X^4 is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};

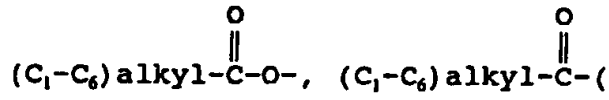
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};

R^{12} is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7)cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10})alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10})alkoxy optionally substituted with

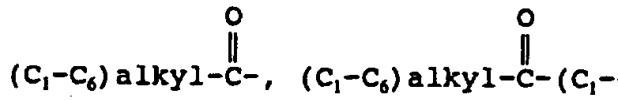
from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino,



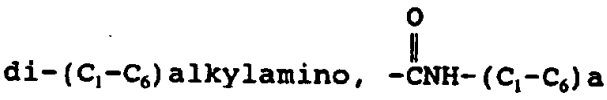
(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl,



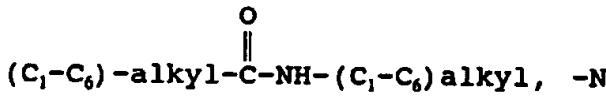
(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,



(C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-,



di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl,

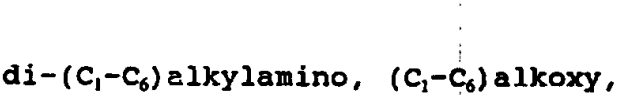


(C_1-C_6)-alkyl-C-NH-(C_1-C_6)alkyl, -NHCH and -NHC-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

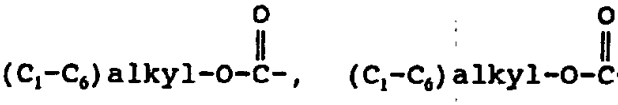
R^{13} is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to it may optionally be replaced by oxygen, nitrogen or sulfur;

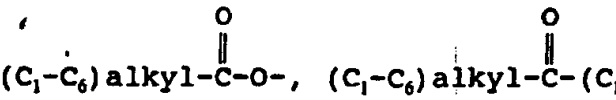
R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino,



di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C-OH,



(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl,



(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,

(C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl-, and the radicals set forth in the definition of R^{12};

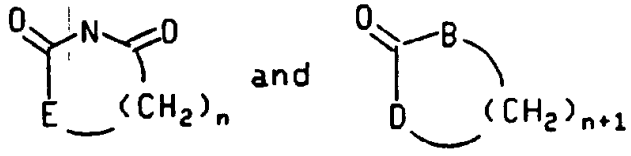
R^{16} is $NH\overset{O}{\overset{\|}{C}}R^{18}$, $NHCH_2R^{18}$, SO_2R^{18}, GR^{20} CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};

R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and

R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

G is selected from the group consisting of CH_2, nitrogen, oxygen, sulfur and carbonyl;

R^{20} is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



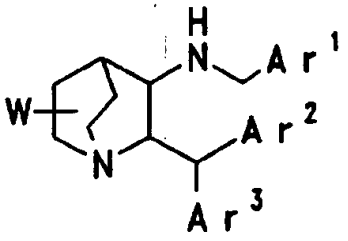
wherein B and D are selected from carbon, oxygen, and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; and any one of the carbons of the $(CH_2)_n$ or $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl, and either any two of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkag , or any one pair of adjacent carbons of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon

atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula VIII, R^{14} and R^{15} cannot be attached to the same carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, (C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} cannot both be hydrogen; (e) when R^{14} or R^{15} is attached to a carbon atom of X^4 or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom; and (f) neither R^{14}, R^{15}, R^{16} nor R^{17} can form a ring with R^{13};

or a pharmaceutically acceptable salt thereof.

3. A method according to claim 1, wherein the compound administered is a compound having the formula



(X)

wherein W is Y or $X(CH_2)_n$;

Y is optionally substituted (C_1-C_6)alkyl, optionally substituted (C_2-C_6)alkenyl or optionally substituted (C_3-C_8)cycloalkyl;

X is optionally substituted (C_1-C_6)alkoxy, hydroxy, $CONR^1R^2$, CO_2R^1, CHR^1OR^2, $CHR^1NR^2R^3$, COR^1, $CONR^1OR^2$ or optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl,

oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl; and n is an integer from zero to six;

Ar^1, Ar^2 and Ar^3 are each, independently, optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl;

and R^1, R^2 and R^3 are independently selected from hydrogen, optionally substituted (C_1-C_6)alkyl, optionally substituted (C_1-C_6)alkoxy, optionally substituted (C_3-C_8)cycloalkyl, optionally substituted aryl, wherein said aryl is selected from phenyl, naphthyl, pyridyl, quinolyl, thienyl, furyl, phenoxyphenyl, oxazolyl, tetrazolyl, thiazolyl, imidazolyl and pyrazolyl; and optionally substituted (C_1-C_5)heterocyclic groups, wherein said heterocyclic groups are selected from pyrrolidino, piperidino, morpholino, piperazinyl and thiamorpholino;

and wherein the substituents on the foregoing substituted alkyl, alkenyl, cycloalkyl and alkoxy groups are independently selected from halo, nitro, amino, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, trifluoromethyl and trifluoromethoxy;

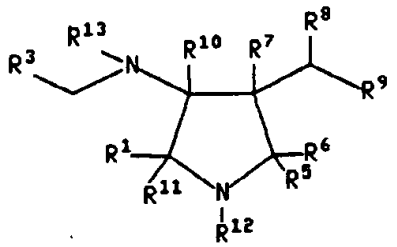
and wherein the substituents on the foregoing substituted (C_1-C_5) heterocyclic groups are attached to a sulfur or nitrogen atom on the ring and are independently selected from oxygen, di-oxygen and (C_1-C_4)alkyl when attached to a ring sulfur atom, and are independently selected from oxygen and (C_1-C_4)alkyl when attached to a ring nitrogen atom;

and wherein the substituents on said substituted Ar^1 groups are independently selected from (C_1-C_6)alkyl optionally substituted with from one to three halo groups, (C_1-C_6)alkoxy optionally substituted with from one to three halo groups, (C_1-C_6)alkylsulfinyl, (C_2-C_6)alkenyl, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylsulfonylamino, and di-(C_1-C_6)alkylamino wherein one or both of the alkyl groups may be optionally substituted with a (C_1-C_6)alkylsulfonyl, or (C_1-C_6)alkylsulfinyl group;

and wherein the substituents on said substituted Ar^2 and Ar^3 groups are independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, (C_1-C_4)alkylsulfinyl, di-(C_1-C_4)alkylamino, trifluoromethyl and trifluoromethoxy; with the proviso that when Y is unsubstituted or is substituted with (C_1-C_4)alkyl, it is attached to the 4- or 6-position of the quinuclidine ring;

or a pharmaceutically acceptable salt of such compound.

4. A method according to claim 1, wherein the compound administered is a compound having the formula

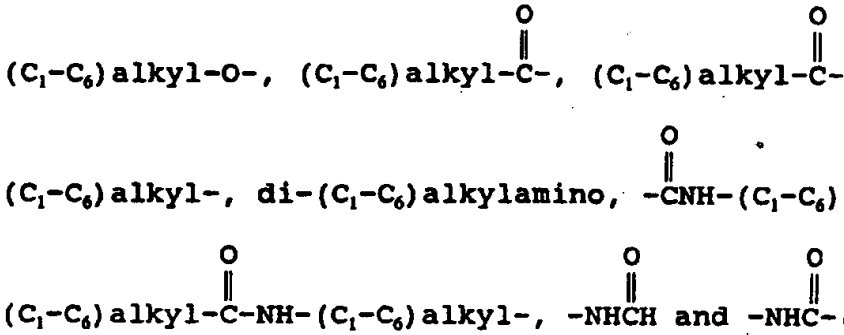


(XI)

wherein R^1 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_1-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy),

(C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-

(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-,

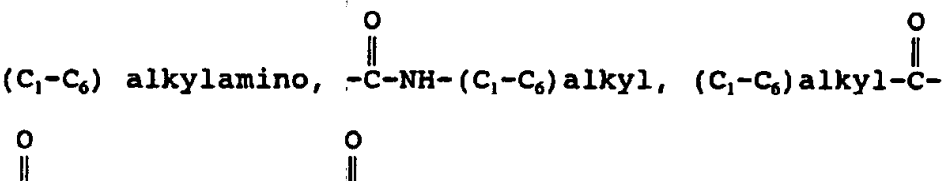


(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-,

(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl,

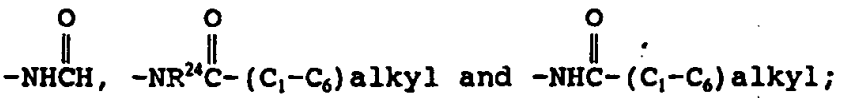
(C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy substituted with from one to three fluorine atoms, amino, phenyl, trihaloalkoxy,



(C_1-C_6) alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-

-C(=O)-O-(C_1-C_6)alkyl, -C(=O)H, $-CH_2OR^{13}$, NH(C_1-C_6)alkyl-,



-NHC(=O)H, $-NR^{24}$C(=O)-(C_1-C_6)alkyl and -NHC(=O)-(C_1-C_6)alkyl;

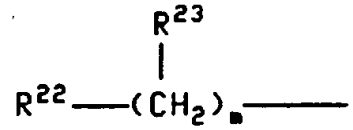
one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, (C_1-C_3)alkyl, (C_1-C_8)acyloxy-(C_1-C_3)alkyl, (C_1-C_8)alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl, $HC(=O)-$, $R^{14}R^{15}NCO_2CH_2-$, $R^{16}OCO_2CH_2-$, (C_1-C_4)alkyl-CO_2CH_2-, $-CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2-$, $R^{19}OCO_2-$, $C_6H_5CH_2CO_2CH_2-$, $C_6H_5CO_2CH_2-$, (C_1-C_4)alkyl-$CH(OH)-$, $C_6H_5CH(OH)-$, $C_6H_5CH_2CH(OH)-$, CH_2halo, $R^{20}SO_2OCH_2$, $-CO_2R^{16}$ and $R^{21}CO_2-$;

R^{10} and R^{11} are independently selected from hydrogen, (C_1-C_3) alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula

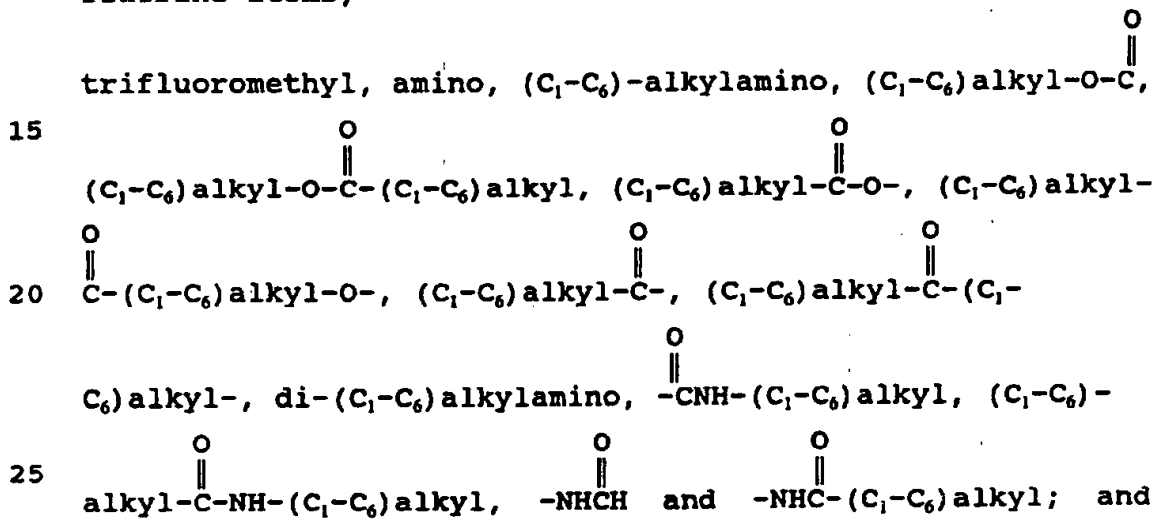


wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^{23};

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)-alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)-alkyl-C(=O)-(C_1-C_6)alkyl, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be r placed by nitrogen, oxygen or sulfur; aryl select d

from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms,

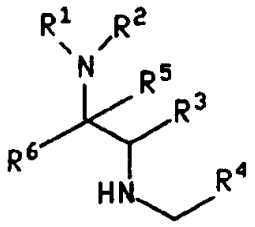


trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHCH(=O) and -NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the proviso that when R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged;

or a pharmaceutically acceptable salt of such compound.

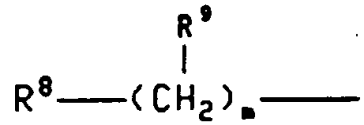
5. A method according to claim 1, wherein the compound administered is a compound of the formula



XII

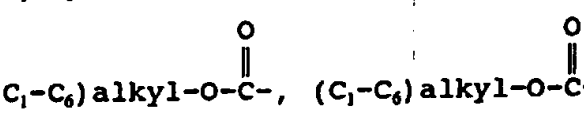
wherein R^1 is hydrogen, (C_1-C_8) alkyl, a saturated (C_6-C_{10}) carbocyclic ring system containing two fused rings, a saturated (C_6-C_{10}) carbocyclic bridged ring system containing two rings, or benzyl wherein the phenyl moiety of said benzyl may optionally be substituted with one or more substituents independently selected from halo, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_8) alkoxy optionally substituted with from one to three fluorine atoms;

R^2 is hydrogen, benzyl or a group of the formula

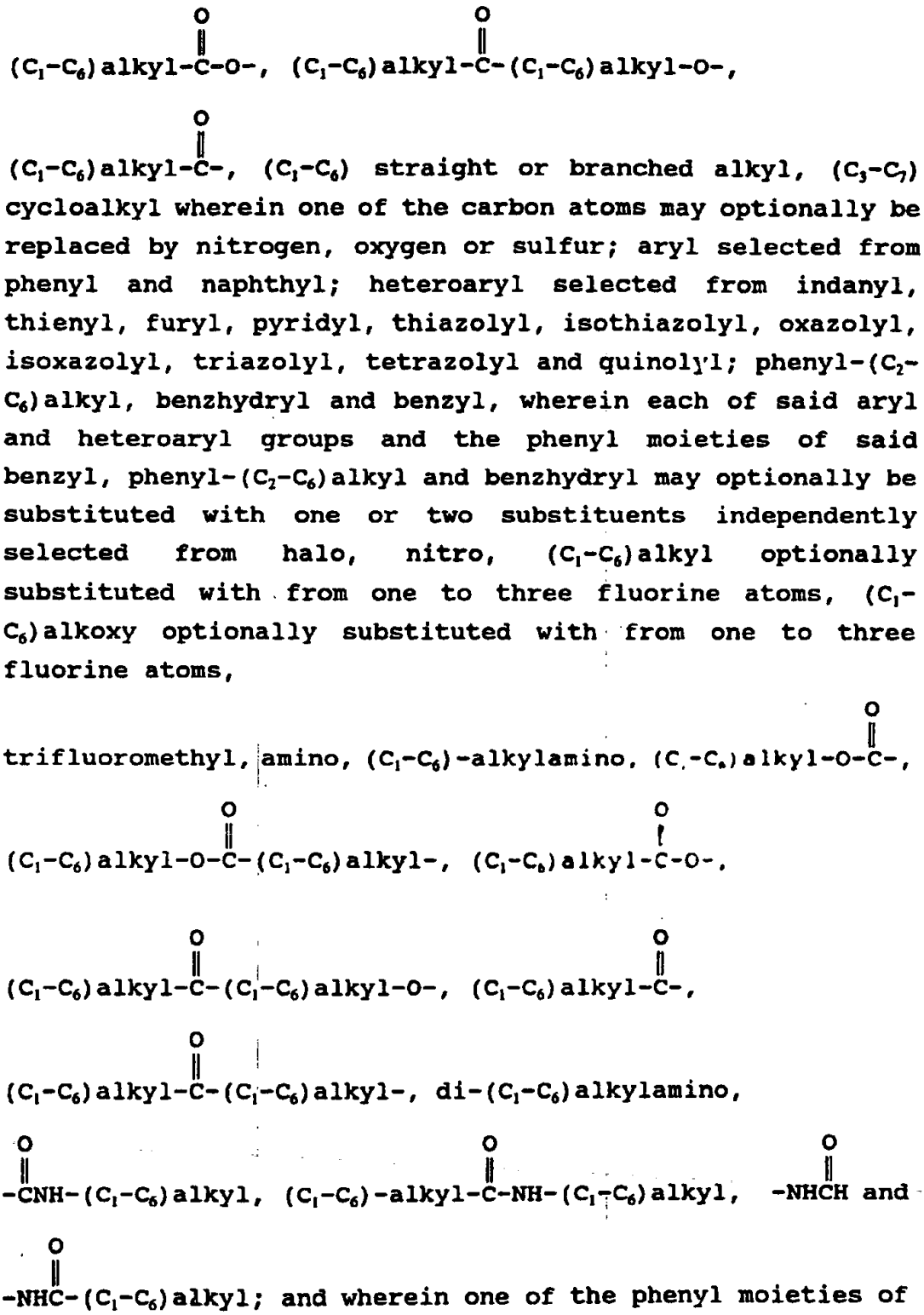


wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^9;

R^8 and R^9 are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy,



(C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl-O-,



(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms,

trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHCH and -NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a saturated or unsaturated monocyclic ring containing from three to eight carbon atoms, a fused bicyclic ring containing from six to ten carbon atoms, or a saturated bridged ring system containing from six to ten carbon atoms;

R^4 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having from three to seven carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one, two or three substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms, phenyl,

amino, (C_1-C_6) alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{O}{\overset{\|}{C}}-$,

$-\overset{O}{\overset{\|}{C}}-O-(C_1-C_6)alkyl$, $-\overset{O}{\overset{\|}{C}}H$, $-CH_2OR^{12}$, $NH_2(C_1-C_6)alkyl-$,

$-NH\overset{O}{\overset{\|}{C}}H$, $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)alkyl$, $-NH-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-(C_1-C_6)alkyl$ and

$(C_1-C_6)alkyl-N(\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-(C_1-C_6)alkyl)$;

R^3 is hydrogen, (C_3-C_8)cycloalkyl, (C_1-C_6) straight or branched alkyl or phenyl optionally substituted with one or more substituents independently selected from halo, (C_1-

C_6)alkyl optionally substituted with from one to three fluorine atoms, and (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

R^5 is hydrogen, (C_1-C_6)alkyl, or phenyl optionally substituted with one or more substituents independently selected from halo, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;

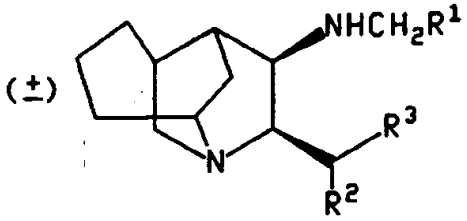
R^6 is selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, trifluoromethyl, amino, trihaloalkoxy (e.g.,trifluoromethoxy), (C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-, -NHC(=O)H and

$-NHC-(C_1-C_6)$alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl; and

R^{12} is hydrogen, (C_1-C_3)alkyl or phenyl;

or a pharmaceutically acceptable salt of such compound.

6. A method according to claim 1, wherein the compound administered is a compound of the formula



XIII

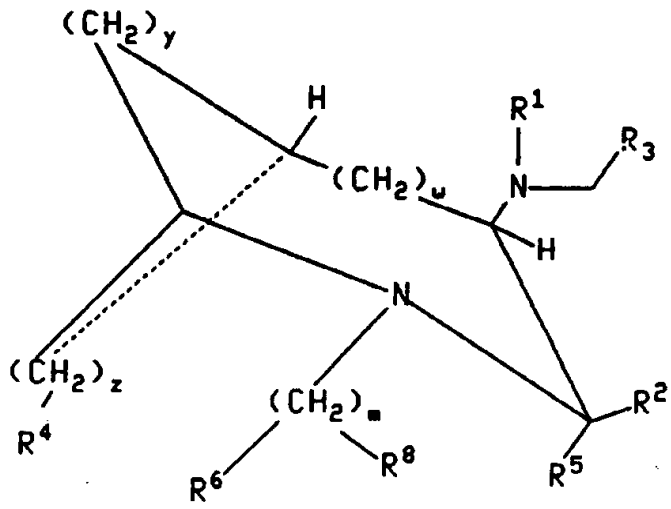
wherein R^1 is cycloalkyl having from five to seven carbon atoms, pyrrolyl, thienyl, pyridyl, phenyl or substituted phenyl, wherein said substituted phenyl is substituted with from one to three substituents independently selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety and benzyloxycarbonyl;

R^2 is furyl, thienyl, pyridyl, indolyl, biphenyl, phenyl or substituted phenyl, wherein said substituted phenyl is substituted with one or two substituents independently selected from fluorine, chlorine, bromine, trifluoromethyl, alkyl having from one to three carbon atoms, alkoxy having from one to three carbon atoms, carboxy, alkoxycarbonyl having from one to three carbon atoms in the alkoxy moiety and benzyloxycarbonyl; and

R^3 is thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;

or a pharmaceutically acceptable salt of such compound.

7. A method according to claim 1, wherein the compound administered is a compound of the formula



XIV

wherein m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

w is an integer from 0 to 2;

y is an integer from 1 to 4;

z is an integer from 1 to 4, and wherein any one of the carbon atoms of said $(CH_2)_z$ may optionally be substituted with R^4;

R^1 is hydrogen or (C_1-C_8) alkyl optionally substituted with hydroxy, alkoxy or fluoro;

R^2 is a group selected from hydrogen, (C_1-C_6)straight or branched alkyl, (C_3-C_7)cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, indanyl, and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl(C_2-C_6)alkyl, benzhydryl and benzyl, wherein on of the phenyl moieties of said benzhydryl may

optionally be replaced by naphthyl, thienyl, furyl or pyridyl and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHCH(=O) and -NHC(=O)-(C_1-C_6) alkyl;

R^5 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^3 is aryl selected from phenyl, indanyl, and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three

fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, phenyl, amino, (C_1-C_6)alkylamino, (C_1-C_6)dialkyl amino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-NH-$(C_1-C_6)$alkyl, $-NH\overset{O}{\overset{\|}{C}}H$ and $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)$alkyl;

R^4 is independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-$\overset{O}{\overset{\|}{C}}$-, (C_1-C_6)alkyl-O-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-O-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl-O-, hydroxy-$(C_1-C_6)$alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl-, and the groups set forth in the definition of R^2;

R^6 is $NH\overset{O}{\overset{\|}{C}}R^9$, $NHCH_2R^9$, $NHSO_2R^9$ or one of the groups set forth in any of the definitions of R^2, and R^4;

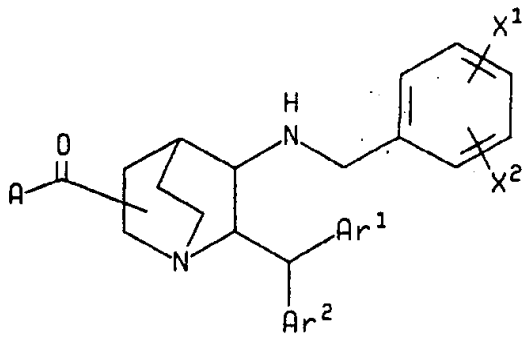
R^8 is oximino (=NOH) or one of the groups set forth in any of the definitions of R^2, and R^4;

R^9 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

with the proviso that (a) when m is 0, R^8 is absent and R^6 is hydrogen, (b) neither R^4, R^6, nor R^8 can form, together with the carbon to which it is attached, a ring with R^5, and (c) the sum of y and z must be less than 7;

or a pharmaceutically acceptable salt thereof.

8. A method according to claim 1, wherein the compound administered is a compound of the formula



XV

wherein X^1 is (C_1-C_5) alkoxy or halosubstituted (C_1-C_5)alkoxy;

X^2 is hydrogen, halogen, (C_1-C_5)alkyl, (C_2-C_5)alkenyl, (C_2-C_5)alkynyl, (C_1-C_5)alkoxy, (C_1-C_5)alkylthio, (C_1-C_5)alkylsulfinyl, (C_1-C_5)alkylsulfonyl, halosubstituted (C_1-C_5)alkyl, halosubstituted (C_1-C_5)alkoxy, (C_1-C_5)alkylamino, dialkylamino having from 1 to 5 carbon atoms in each alkyl moiety, (C_1-C_5)alkylsulfonylamino (which may be substituted by halogen), (C_1-C_5)alkyl-N-(C_1-C_5)alkylsulfonyl (which may be substituted by halogen in the alkylsulfonyl moiety), (C_1-C_5)alkanoylamino (which may be substituted by halogen) or (C_1-C_5)alkyl-N-(C_1-C_5)alkanoyl (which may be substituted by halogen in the alkanoyl moiety);

Ar^1 and Ar_2 are each, independently, thienyl, phenyl, fluorophenyl, chlorophenyl or bromophenyl;

A is $Y-(CH_2)_m-CH(R^2)-(CH_2)_n-NR^1-$;

R^1 is hydrogen, (C_1-C_5)alkyl, benzyl or $-(CH_2)_p-Y$;

R^2 is hydrogen, (C_1-C_5)alkyl (which may be substituted by a substituent selected from the group consisting of hydroxy, amino, methylthio and mercapto), benzyl, 4-hydroxybenzyl, 3-indolylmethyl or $-(CH_2)_p-Y$;

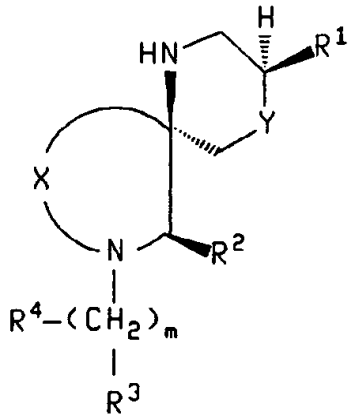
Y is -CN, $-CH_2Z$ or -COZ;

Z is hydroxy, amino, (C_1-C_5)alkoxy, (C_1-C_5)alkylamino or dialkylamino having from 1 to 5 carbon atoms in each alkyl moiety;

m, n and p are each, independently, 0, 1, 2 or 3; and R^1 and R^2 may be connected to form a ring;

or a pharmaceutically acceptable salt thereof.

9. A method according to claim 1, wherein the compound administered is a compound of the formula



XVI

wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino,

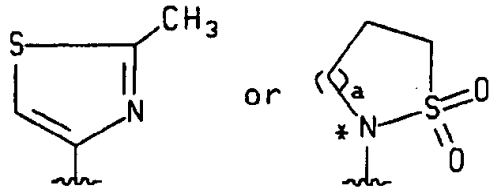
di-(C_1-C_6)alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$alkyl,

(C_1-C_6)alkyl$-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)$ alkyl, hydroxy(C_1-C_4)alkyl,

$-\overset{O}{\overset{\|}{NHCH}}$, $-\overset{O}{\overset{\|}{NHC}}-(C_1-C_6)$ alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-S(O)_v-(C_1-C_{10})$-alkyl wherein v is zero, one or two, $-S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, $-SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5,

together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, (C_1-C_{10})alkyl-$\overset{|}{N}$-SO_2-(C_1-C_{10})alkyl wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and (C_1-C_{10})alkyl-$\overset{|}{N}$-SO_2-aryl; and wherein the aryl moieties of said $-S(O)_v$-aryl, -O-aryl and (C_1-C_{10})alkyl-$\overset{|}{N}$-SO_2-aryl are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;

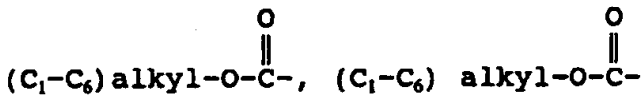
or R^1 is phenyl substituted with a group having the formula



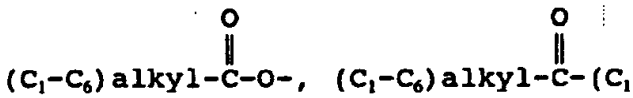
wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R^1;

R^2 is selected from (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro,

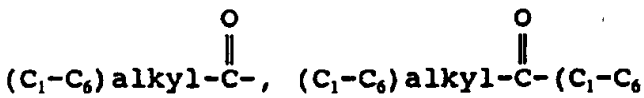
(C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino,



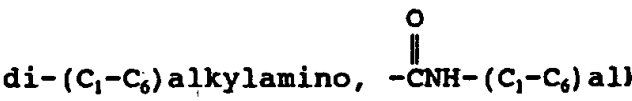
(C_1-C_6)alkyl-O-C-, (C_1-C_6) alkyl-O-C-(C_1-C_6)alkyl,



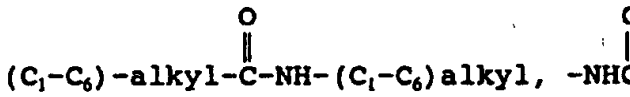
(C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-,



(C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-,



di-(C_1-C_6)alkylamino, -CNH-(C_1-C_6)alkyl,



(C_1-C_6)-alkyl-C-NH-(C_1-C_6)alkyl, -NHCH and -NHC-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;

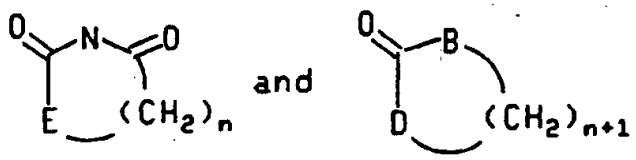
R^3 is selected from NHCR^8, NHCH_2R^8, SO_2R^8, AR^9, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;

A is CH_2, nitrogen, oxygen, sulfur or carbonyl;

R^8 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

R^4 is selected from oximino (=NOH) and the radicals s t forth in the definitions of R^2, R^6 and R^7;

R^9 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;

R^6 and R^7 are independently selected from hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino,

di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, ,

(C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,

(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-,

(C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl- and the radicals set forth in the definition of R^2; and

Y is $(CH_2)_z$ wherein z is zero or one;

with the proviso that: (a) when A is $-(CH_2)-$ or carbonyl, R^9 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; and (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom;

or a pharmaceutically acceptable salt of such compound.

10. A method according to claim 2, wherein the compound administered to said mammal is selected from the group consisting of:

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;

(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine;

phenylmethyl

(2S,3S)-3(-5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

2-(diphenylmethyl)-N-(2-methoxy-5-trifluoromethoxy-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine;

(2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-difluoromethoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine;

(2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxybenzyl)-aminopiperidine;

(2S,3S)-2-phenyl-3-(2-trifluoromethoxybenzyl)]aminopiperidine;

and the pharmaceutically acceptable salts of the foregoing compounds.

11. A method according to claim 2, wherein the compound administered to said mammal is selected from the group consisting of:

cis-3-(2-chlorobenzylamino)-2-phenylpiperidine;

cis-3-(2-trifluoromethylbenzylamino)-2-phenyl-piperidine;

cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(2-chlorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(2-methylphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-methoxyphenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-chlorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(2-methoxybenzylamino)-2-(3-methylphenyl)-piperidin ;

cis-3-(2-methoxybenzylamino)-2-(4-fluorophenyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-(3-thienyl)-piperidine;

cis-3-(2-methoxybenzylamino)-2-phenylazacyclo-heptane;
3-(2-methoxybenzylamino)-4-methyl-2-phenylpiperidine;
3-(2-methoxybenzylamino)-5-methyl-2-phenylpiperidine;
3-(2-methoxybenzylamino)-6-methyl-2-phenylpiperidine;
(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-(5-carboethoxypent-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-(6-hydroxy-hex-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-(4-hydroxy-4-phenylbut-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-(4-oxo-4-phenylbut-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-(5,6-dihydroxyhex-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
cis-3-(5-fluoro-2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-[4-(4-fluorophenyl)-4-oxobut-1-yl]-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-[4-[4-fluorophenyl)-4-hydroxybut-1-yl]-3-(2-methoxybenzylamino)-2-phenylpiperidine;
cis-3-(2-methoxy-5-methylbenzylamino)-2-phenylpiperidine;
(2S,3S)-1-(4-benzamidobut-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
cis-3-(2-methoxynaphth-1-ylmethylamino)-2-phenylpiperidine;
(2S,3S)-3-(2-methoxybenzylamino)-1-(5-N-methylcarboxamidopent-1-yl)-2-phenylpiperidine;
(2S,3S)-1-(4-cyanobut-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-[4-(2-naphthamido)but-1-yl]-3-(2-methoxybenzylamino)-2-phenylpiperidine;
(2S,3S)-1-(5-benzamidop nt-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-1-(5-aminopent-1-yl)-3-(2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-3-(5-chloro-2-methoxybenzylamino)-2-phenylpiperidine;

(2S,3S)-3-(2,5-dimethoxybenzylamino)-2-phenylpiperidine;

cis-3-(3,5-difluoro-2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(4,5-difluoro-2-methoxybenzylamino)-2-phenylpiperidine;

cis-3-(2,5-dimethoxybenzylamino)-1-[4-(4-fluorophenyl)-4-oxobut-1-yl]-2-phenylpiperidine;

cis-3-(5-chloro-2-methoxybenzylamino)-1-(5,6-dihydroxyhex-1-yl)-2-phenylpiperidine;

cis-1-(5,6-dihydroxyhex-1-yl)-3-(2,5-dimethoxybenzylamino)-2-phenylpiperidine;

cis-2-phenyl-3-[-2(prop-2-yloxy)benzylamino]piperidine;

cis-3-(2,5-dimethoxybenzyl)amino-2-(3-methoxyphenyl)piperidine hydrochloride;

cis-3-(5-chloro-2-methoxybenzyl)amino-2-(3-methoxyphenyl)piperidine dihydrochloride;

cis-3-(5-chloro-2-methoxybenzyl)amino-2-(3-chlorophenyl)piperidine dihydrochloride;

3-(2-methoxybenzylamino)-2,4-diphenylpiperidine;

cis-3-(2-methoxybenzylamino)-2-phenylpyrrolidine;

(2S,3S)-3-(5-ethyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-n-butyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-methoxy-5-n-propylbenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-isopropyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-s-butyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-t-butyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-methoxy-5-phenylbenzyl)amino-2-phenylpiperidine;

and the pharmaceutically acceptable salts of the foregoing compounds.

12. A method according to claim 2, wherein the compound administered to said mammal is selected from the group consisting of:

2,4-dimethylthiazole-5-sulfonic acid [4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-methylamide;

N-(4,5-dimethylthiazol-2-yl)-N-[4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-yl-aminomethyl)phenyl]-methanesulfonamide;

{5-[(4,5-dimethylthiazol-2-yl)methylamino]-2-methoxybenzyl}-((2S,3S)-2-phenylpiperidin-3-yl)amine;

{5-(4,5-dimethylthiazol-2-ylamino)-2-methoxybenzyl}-((2S,3S)-2-phenylpiperidin-3-ylamine;

4,5-dimethylthiazole-2-sulfonic acid methyl-[3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)-4-trifluoromethoxyphenyl]-amide;

2,4-dimethylthiazole-5-sulfonic acid [4-isopropoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-methylamide;

2,4-dimethylthiazole-5-sulfonic acid [4-isopropoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-isopropylamide;

2,4-dimethylthiazole-5-sulfonic acid [4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-isopropylamide;

2,4-dimethylthiazole-5-sulfonic acid [4-methoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)phenyl]-isobutylamide;

2,4-dimethylthiazole-5-sulfonic acid [4-isopropoxy-3-((2S,3S)-2-phenylpiperidin-3-ylaminomethyl)ph nyl]-isobutylamide;

and the pharmaceutically acceptable salts of the foregoing compounds.

13. A method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, comprising administering to said mammal an amount of a compound selected from the group consisting of:

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-methyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-sec-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine; and

(2S,3S)-N-(5-n-propyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine,

and the pharmaceutically acceptable salts of the foregoing compounds, that is effective in treating or preventing such disorder.

14. A method according to claim 3, wherein the compound administered to said mammal is selected from the group consisting of:

(3R,4S,5S,6S)-N,N-diethyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-N,N-diethyl-5-(2,5-dimethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide;

(3R,4S,5S,6S)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-2-methylthiobenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2,5-dimethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo-[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-ethyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxyl-5-n-propylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-sec-butyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-N-methyl-methanesulfonylamino-2-methoxy-benzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfinylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-trifluoromethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfonylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-dimethylamino-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid;

(3R,4S,5S,6S)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylthiobenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2,5-dimethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(5-ethyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxyl-5-n-propylbenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(5-sec-butyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(5-N-methyl-methanesulfonylamino-2-methoxybenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfinylbenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-trifluoromethoxybenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(2-methoxy-5-methylsulfonylbenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

(3R,4S,5S,6S)-5-(5-dimethylamino-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-2-carboxylic acid;

and the pharmaceutically acceptable salts of the foregoing compounds.

15. A method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, comprising administering to said mammal an amount of a compound that is an NK-1 receptor antagonist, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder.

16. A method of treating or preventing a disorder of the eye selected from glaucoma, ocular hypertension, miosis, hyperemia, excess lacrimation and breakdown of the blood aqueous barrier in a mammal, comprising administering to said mammal an amount of a compound that is an substance P receptor antagonist, or a pharmaceutically acceptable salt

thereof, that is effective in treating or preventing such disorder.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 95/00811

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K31/435 A61K31/55 A61K31/40 A61K31/135
A61K31/675

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 216, 1992 pages 327-329, Z. WANG ET AL. 'THE ELECTRICALLY EVOKED, TACHYKININ-MEDIATED CONTRACTILE RESPONSE OF THE ISOLATED RABBIT IRIS SPHINCTER MUSCLE INVOLVES NK1 RECEPTORS ONLY' see the whole document ---	1,2,15, 16
X	BRITISH JOURNAL OF PHARMACOLOGY, vol. 111, no. 1, January 1994 pages 179-184, Z. WANG ET AL. 'NON-SPECIFIC ACTIONS OF THE NON-PEPTIDE TACHYKININ RECEPTOR ANTAGONISTS, CP-96,345, RP67580 AND SR 48968, ON NEUROTRANSMISSION' see the whole document ---	1,2,15, 16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 1996	23.02.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Hoff, P

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/IB 95/00811

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 178, no. 1, 1991 pages 297-301, R. HAKANSON ET AL. 'COMPARISON OF SPANTIDE II AND CP-96,345 FOR BLOCKAGE OF TACHYKININ-EVOKED CONTRACTIONS OF SMOOTH MUSCLE' see the whole document	1,2,15, 16
X	BRITISH JOURNAL OF PHARMACOLOGY, vol. 107, 1992 pages 762-765, Z. WANG ET AL. 'CP-96,345, A SELECTIVE TACHYKININ NK1 RECEPTOR ANTAGONIST, HAS NON-SPECIFIC ACTIONS ON NEUROTRANSMISSION' see the whole document	1,2,15, 16
X	SCIENCE, vol. 214, 1981 pages 1029-1031, G. HOLMDAHL ET AL. 'SUBSTANCE P ANTAGONIST, (D-PRO, D-TRP)SP, INHIBITS INFLAMMATORY RESPONSES IN THE RABBIT EYE' cited in the application	15,16
Y	see the whole document	1-4,6-8, 10-14
X	JOURNAL OF IMMUNOLOGY, vol. 135, no. 2, 1985 pages 812S-815S, B. PERNOW 'ROLE OF TACHYKININS IN NEUROGENIC INFLAMMATION' see abstract	15,16
Y	see page 814S	1-4,6-8, 10-14
X	FERNSTRÖM FOUNDATION SERIES, vol. 6, 1985 pages 91-96, R. HAKANSON ET AL. 'TACHYKININ ANTAGONISTS SUPRESS RESPONSE TO OCULAR INJURY IN THE RABBIT'	15,16
Y	see the whole document	1-4,6-8, 10-14
Y	EP,A,0 610 021 (PFIZER INC.) 10 August 1994 see page 2, line 1 - line 17 see page 35, line 48 - page 36, line 43; claims	1-4,6-8, 10,11, 13,14

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/IB 95/00811

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO,A,95 07908 (PFIZER INC.) 23 March 1995 cited in the application see abstract see page 1, line 1 - line 18; claims	1,2,12
Y	WO,A,94 08997 (PFIZER INC.) 28 April 1994 cited in the application see abstract see page 1, line 1 - line 14; claims	1
Y	WO,A,94 10170 (PFIZER INC.) 11 May 1994 cited in the application see abstract see page 1, line 1 - line 14; claims	1
P,Y	WO,A,94 26740 (PFIZER INC.) 24 November 1994 cited in the application see abstract see page 1, line 1 - line 11; claims	1
P,Y	WO,A,95 07886 (PFIZER INC.) 23 March 1995 cited in the application see abstract see page 1, line 1 - line 9; claims	1
X	EP,A,0 533 280 (GLAXO GROUP LIMITED) 24 March 1993 see abstract see page 17, line 25 - line 30; claims	1,2
X	WO,A,94 16697 (RHONE-POULENC RORER) 4 August 1994 see abstract see page 1, line 26 - page 2, line 8 see page 39, line 20 - page 40, line 3 see page 48, line 1 - line 16; claims	1,2,11

3

...ernational application No.

PCT/IB 95/00811

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Please see enclosed form!

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see enclosed form!

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please see enclosed information!

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,15,16 partly; 2-4,6-8,10-14 completely

Remark on Protest

[ ] The additional search fees were accompanied by the applicant s protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 95/ 00811

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

LACK OF UNITY OF INVENTION

The problem the application tries to solve is to treat or prevent a disorder of the eye (glaucoma, ocular hypertension, miosis, excess of lacrimation, hyperemia and breakdown of the blood aqueous barrier).
The proposed solution is to use substance P/NK-1 receptor antagonists especially

- compounds of formulas Ia,Ib,Ic,Id,Ie (with P=NR_2), X, XI, XIII, XIV, XV, XVII, XVIII, XIX, XXI characterised by an arylmethylamine moiety attached to a saturated aminoheterocyclic ring
- ethylene diamine compounds such as described by the general formula XII
- spiroazacyclic compounds such as described by the general formula XVI
- compounds of formulas Ie (with P=0), XX characterised by an arylmethyloxy moiety attached to a saturated aminoheterocyclic ring
- compounds of formula Ie (with P=S,SO,SO_2)

Their pharmacological properties (substance P/NK-1 antagonists) represent the technical features which may a priori, unify the different groups of compounds.
The documents: -Science, vol. 214, 1981, p. 1029-1031
-the J. of Immunol., vol. 135, 1985, p.8125-8155
-Fernstr. Found. Series, vol. 6, 1985, p. 91-96
describe substance P receptor antagonists which inhibit the response to ocular trauma (miosis, hyperemia, breakdown of the blood-aqueous barrier, ocular hypertension).

Furthermore, documents
- Europ. J. Pharmacol., vol. 216, 1992, p. 327-329
- Br. J. Pharmacol., vol. 111, 1/94, p. 179-184
- Br. J. Pharmacol., vol. 107, 1992, p. 762-765
- Biochem. Biophys. Res. Comm., 1991, p. 297-301

disclose the antimiotic activity of an substance P/NK-1 receptor antagonist: CP-96345.
Because a solution based on technical features identical to those forwarded in the present application (see page 1, lines 1-17) has already been disclosed (see cited documents above), these technical features proposed in the present application cannot be accepted as special technical features involved in the technical relationship among the different inventions.
As no other special technical features can be distinguished which could fulfil this requirement in the light of the prior art, there is no single inventive concept underlying th plurality of different inventions of the present application. (see rule 13.1 PCT).
Consequently there is lack of unity a posteriori and the different inventions not belonging to a common inventive concept (in the light of the prior art), are formulated as the different subjects n the communication pursuant to Art. 17(3)(a)PCT.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Furthermore, searching this plurality of different subjects would have caused "major additional searching efforts".

1. Claims searched: 1,15,16 (partially)
   2-4,6-8,10-14 (completely)
   Use of compounds of formulas Ia, Ib, Ic, Id, Ie (P=NK2), X, XI, XIII, XIV, XV, XVII, XVIII, XIX, XXI for heating a disorder of the eye.
2. Claims not searched: 1,15,16 (partially)
   5 (completely)
   Use of compounds of formula XII for treating a disorder of the eye
3. Claims not searched: 1,15,16 (partially)
   9 (completely)
   Use of compounds of formula XVI for treating a disorder of the eye
4. Claims not searched: 1,15,16 (partially)
   Use of compounds of formulas Ie (P=O), XX for treating a disorder of the eye
5. Claims not searched: 1,15,16 (partially)
   Use of compounds of formula Ie (P=S, SO, SO2) for treating a disorder of the eye.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IB 95/00811

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

INCOMPLETE SEARCH

Claims searched completely: 10-14
Claims searched incompletely: 1-4,6-8,15-16

A compound cannot be sufficiently characterised by its pharmacological profile or its mode of action as it is done by expressions like "substance P receptor antagonists" or "NK-1 receptor antagonists".
In view of the large number of compounds which are defined by the general formulas of claims 1-4,6-8, the search was limited to the inventive part of the molecules and to the compounds specifically mentioned in the description and in the claims (PCT: Art. 6; Guidelines ... Part B, Chapt. II.7 last sentence and Chapt. III, 3.7).

Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/IB 95/00811

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-610021	10-08-94	US-A-	5340826	23-08-94
WO-A-9507908	23-03-95	AU-B-	7082194	03-04-95
		FI-A-	944310	18-03-95
WO-A-9408997	28-04-94	JP-A-	6135963	17-05-94
		AU-B-	5165393	09-05-94
		EP-A-	0665844	09-08-95
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		HU-A-	65133	28-04-94
WO-A-9410170	11-05-94	JP-A-	6135964	17-05-94
		AU-B-	5141293	24-05-94
		CA-A-	2146007	11-05-94
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WO-A-9426740	24-11-94	AU-B-	6691094	12-12-94
		CA-A-	2161886	24-11-94
		FI-A-	942314	20-11-94
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EP-A-533280	24-03-93	AU-B-	657996	30-03-95
		AU-B-	2458392	25-03-93
		CA-A-	2078578	21-03-93
		JP-A-	6107563	19-04-94
		US-A-	5360820	01-11-94
		ZA-A-	9207156	18-03-94
WO-A-9416697	04-08-94	FR-A-	2700472	22-07-94
		AU-B-	5862794	15-08-94
		BE-A-	1006705	22-11-94
		CA-A-	2152401	04-08-94
		EP-A-	0680323	08-11-95
		GB-A-	2274777	10-08-94
		LU-A-	88442	03-10-94
		NO-A-	952828	17-07-95
		PT-A-	101444	31-10-94